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POLYCYTHAEMIA VERA

REPORT OF A CASE

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In May 1783, when Harvard Medical School was in its infancy, Dr. Benjamin Waterhouse presented a paper before the American Academy of Arts and Sciences. This was the first communication to any scientific body from a member of the faculty of Harvard Medical School and therefore may be regarded as an important foundation stone on which have been superimposed all subsequent medical publications by graduates of this school. At that time he said in nearly these words:

> I appeal to every practitioner who like me has anxiously turned over the observations of others in hopes of finding something to guide him in a case which puzzles him to commit to writing the observations which he makes in order that an exact account of a hitherto inexplicable disorder may be transmitted to his successors.

With this precept in mind the following account of a case of polycythaemia vera is recorded. The case appears unusual in that so far as can be determined it is the first example of the disease to be described in which the clinical picture of polycythaemia vera was seen to develop in a person previously regarded as normal, in which its clinical earmarks disappeared under treatment and in which, finally, it left behind a variety of interesting vestiges of its previous existence.

REPORT OF CASE

In 1930 H. S., a 50 year old physician of Yankee breeding, presented himself for physical examination. He was a hard working practitioner, was well so far as he knew and had been free of any serious illness in the past beyond an attack of pneumonia ten years before. His only complaint was that for many years he had suffered from attacks of migraine, never producing sufficiently bad headaches to interfere with his work but of late becoming more frequent and being accompanied by nausea and vomiting.

The results of his general physical examination were unremarkable. The blood pressure was 140 mm. systolic and 80 mm. diastolic. Retinal examination revealed well outlined disk margins and normal-appearing vessels. The peripheral vessels seemed normal. The urine was free of albumin and sugar and contained an occasional leukocyte in the sediment. The hemoglobin concentration was 90 per cent. The red and the white cells were normal in appearance. The Wassermann reaction was negative.

The patient felt well for the next four years. Then he returned for rechecking. He had gained 14 pounds (6.5 Kg.) in the interval. He was a little concerned, he said, because his blood pressure was "climbing up," and because recently when he examined his own urine, he found that it contained "plenty of albumin and casts."

During the past four years his headaches had decreased in intensity. He remarked that he believed his peripheral vessels were becoming tortuous and sclerosed, and he feared that he was becoming generally arteriosclerotic, because he seemed to tire out more easily on less work and in general to feel less energetic than he would like. But on the whole he had no striking complaints.

His appearance was about as it had been except that he now appeared rather flushed and had a suggestion of puffiness around the eyes. The heart was not hypertrophied, and the eyegrounds failed to show any obvious vascular lesions. The blood pressure was 160 mm. systolic and 80 mm. diastolic. The peripheral vessels were, in fact, palpable, though it was difficult to measure how much they had changed since the first observation. The spleen was not felt. A specimen of urine excreted during the day contained 350 mg. of albumin per liter, while a sample of urine excreted during the night was albumin free. Neither specimen contained sugar or casts. The concentration of nonprotein nitrogen in the blood was 34 mg. per hundred cubic centimeters. Unfortunately, no blood counts were made.

In 1935, a year and a half later, he appeared for the third time. He had lost 11 pounds (5 Kg.) in weight since his last visit for no reason that he knew. He was convinced that his systolic blood pressure now was in the neighborhood of 180 mm. most of the time. More particularly, however, he had begun gradually to experience persistent and disabling headaches, not of the migrainous type but more continuous, often waking him up at night and lasting for two or three days. Along with this he noticed that his memory was failing, that his face flushed easily and often looked so red as to make him feel self conscious and that he had reddish blue hands and feet, which were often painful, characteristic, in his opinion, of erythromelalgia.

On physical examination his face was flushed and bluish red. The eyegrounds did not show any especially noticeable vascular lesions, but the veins were overfull and distended. The heart was normal, although, as the patient had observed, the systolic blood pressure was 180 mm. The spleen was enlarged, so that its edge was easily felt. The urine contained 4.0 Gm. of albumin per liter and contained in the sediment many hyaline casts and a few leukocytes. The hemoglobin concentration was 145 per cent, and the red cell count was 8,800,000. The hematocrit reading showed that nearly 80 per cent of the volume of the blood was corpuscular.

Comment.—In this fashion the polycythemia became apparent, so insidiously as to make its exact mode of onset uncertain and so gradually as to make it impossible to say in retrospect whether it commenced one, three or five years before it was recognized. Because arterio-

sclerotic changes in the peripheral vessels and hypertension also had advanced in the same insidious fashion during observation, one could not help but wonder whether whatever caused the vascular disease, on the one hand, had not caused the polycythemia, on the other, or whether the clinical blossoming of polycythemia was not, in fact, a local manifestation of a general vascular disorder.

Even a single case in which polycythemia is seen to develop as it did in this one disposes whoever observes the phenomenon to place a good deal of weight on the studies of Reznikoff, Foot and Bethea.[1] They claimed that if the bone marrow of a patient with polycythemia is studied by appropriate staining methods there often can be demonstrated in it such vascular changes as thickening of its capillary walls and subintimal or adventitial fibrosis of its arteries and arterioles, a state of affairs well able to produce chronic anoxemia of the bone marrow and resultant polycythemia. Some such lesion as this, it seemed, might well have developed in our case.

In any event a definite diagnosis was established, and the question of treatment arose. The most appropriate management of polycythemia is somewhat confusing to select; any practitioner who turns to the observations of other investigators on this point, in hopes of finding something to guide him in a case which puzzles him, will discover that opinions nowadays differ and perhaps are recorded by personal friends, so that unbiased judgment may be difficult. Our fellow Bostonian, Dr. Joseph H. Pratt, and his associate Morawitz[2] deserve credit for suggesting in 1908 that phenylhydrazine might be a useful drug to administer when destruction of blood is desirable. No one who has visited the Mayo Clinic can help but be impressed by the results obtained there with phenylhydrazine in the treatment of polycythemia, as reported by Giffin and his associates.[3] On the other hand, there are other methods which have been used with equal success. For many years Haden,[4] of the Crile Clinic, Cleveland, has upheld stoutly that intelligent venesection, with due attention to the total blood volume, is the therapeutic method of choice. Irradiation with roentgen rays

1. Reznikoff, P.; Foot, N. C., and Bethea, J. M.: Etiologic and Pathologic Factors in Polycythemia Vera, Am. J. M. Sc. **189**:753-759 (June) 1935.

2. Morawitz, P., and Pratt, J.: Einige Beobachtungen bei experimentellen Anämien, München. med. Wchnschr. **55**:1817-1819 (Sept. 1) 1908.

3. Brown, G. E., and Giffin, H. Z.: The Treatment of Polycythemia Vera (Erythremia) with Phenylhydrazine, Arch. Int. Med. **38**:321-345 (Sept.) 1926. Giffin, H. Z., and Allen, E. V.: The Control and Complete Remission of Polycythemia Vera Following the Prolonged Administration of Phenylhydrazine Hydrochloride, Am. J. M. Sc. **185**:1-12 (Jan.) 1933.

4. Haden, R. L.: The Red Cell Mass in Polycythemia in Relation to Diagnosis and Treatment, Am. J. M. Sc. **196**:493-502 (Oct.) 1938.

or radioactive phosphorus, as demonstrated recently by Lawrence,[5] can be useful, or if one is more conservative, arsenic in the form of solution of potassium arsenite U. S. P. (Fowler's solution), as employed by Forkner, Scott and Wu,[6] may be of measurable service. Proper regulation of diet, it is almost generally agreed, must always be advised, as the value of a low iron diet has been repeatedly emphasized. Dameshek and Henstell[7] have described the details of a practical diet for the treatment of polycythemia.

On the whole, in reviewing the experience of other investigators in the treatment of polycythemia it was fairly evident that a diet low in iron combined in some fashion with solution of potassium arsenite, bleeding, administration of phenylhydrazine or irradiation were the four most popular methods of treatment then in vogue, each having respectable proponents and opponents. To our way of thinking at the time, phenylhydrazine had certain disadvantages, as emphasized by Giffin and Conner[8]; all were particularly noteworthy for our patient, since one of us (R. F.) had lately encountered an elderly patient with marked arteriosclerosis who was unduly sensitive to the drug and in whom nearly fatal hemolytic anemia, complicated by thrombosis of the splenic vein, developed after phenylhydrazine therapy.

The bleeding technic, as outline by Haden, seemed simple and rational enough, but the patient himself voted against it. He was familiar with two pieces of work which had been talked of in Boston and which had impressed his mind: one by Forkner and his colleagues, on the beneficial use of solution of potassium arsenite in the treatment of certain patients with polycythemia, and the other by Minot and Buckman,[9] who described 3 patients who had been polycythemic for several years and in whom a profound degree of anemia eventually developed. He said if there was any possibility of his having a disease which began with polycythemia and ended with anemia, his own blood might some day be useful to him and he would like to keep it for a while. He preferred at first to follow a therapeutic program which was as harmless as possible and yet at the same time was based on sound principles. To his way of thinking clinical trial for

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5. Lawrence, J. H.: Nuclear Physics and Therapy: Preliminary Report on a New Method for the Treatment of Leukemia and Polycythemia, Radiology **35**:51-60 (July) 1940.

6. Forkner, C. E.; Scott, T. F. M., and Wu, S. C.: Treatment of Polycythemia Vera (Erythremia) with Solution of Potassium Arsenite, Arch. Int. Med. **51**:616-629 (April) 1933.

7. Dameshek, W., and Henstell, H. H.: Diagnosis of Polycythemia, Ann. Int. Med. **13**:1360-1387 (Feb.) 1940.

8. Giffin, H. Z., and Conner, H. M.: The Untoward Effects of Treatment by Phenylhydrazine Hydrochloride, J. A. M. A. **92**:1505-1507 (May 4) 1929.

9. Minot, G. R., and Buckman, T. E.: Erythremia (Polycythemia Rubra Vera), Am. J. M. Sc. **166**:467-489 (May) 1923.

a reasonable length of time of a compound containing arsenic supplemented by a low iron diet seemed most satisfactory. Accordingly, he began to diet and to take solution of potassium arsenite U. S. P. (Fowler's solution).

The effect of this part of his treatment is difficult to evaluate. It appeared to be partially effective but was by no means entirely successful.

Apparently the solution of potassium arsenite brought about a slight fall in hemoglobin, red cell count and hematocrit reading. Perhaps the spleen grew a little smaller. There was no significant change in the level of body weight or blood pressure. The patient felt better, but on the other hand, he began having attacks of angina pectoris, which worried him, and he had an attack of herpes zoster, followed

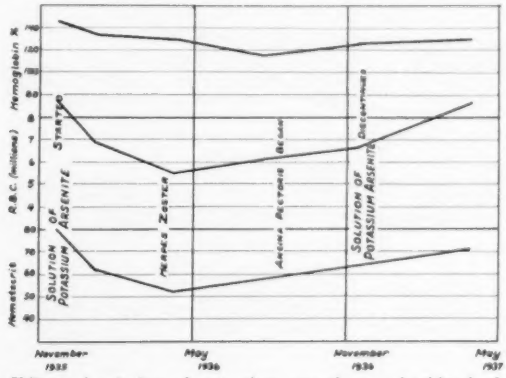

Fig. 1.—Effect of solution of potassium arsenite on the blood of a patient with polycythaemia vera.

later, after therapy with solution of potassium arsenite had been stopped and then reinstated, by a dark-looking skin and a certain amount of chronic indigestion. Having taken potassium arsenite for a year, with only the improvements just mentioned, he rested for four months from all treatment other than diet and at the end of March 1937 declared himself ready to try another therapeutic approach.

In June 1936 there had been published in the *New England Journal of Medicine* a paper by Hunter,[10] of the Massachusetts General Hospital, which attracted considerable attention locally. This dealt with "spray" radiation therapy and included reports of 2 cases in which Hunter had used this method in treating patients with polycythemia and had followed them carefully for three years afterward. The results which were obtained seemed promising. The patient knew of this

10. Hunter, F. T.: "Spray X-Ray Therapy" in Polycythemia Vera and in Erythroblastic Anemia, New England J. Med. **214**:1123-1127 (June 4) 1936.

paper; he admired Dr. George W. Holmes and the Massachusetts General Hospital, and he therefore decided on a course of roentgen therapy under the hands of that roentgenologist at that institution. He received seven treatments between April 3 and 12, 1937 in daily doses of 70 r and five treatments beginning May 4 and ending May 8 in daily doses of 70 r. Thus, he received a total dose of 840 r. The rays were sprayed on the anterior and the posterior surface of the body on alternating days over an area which included the entire trunk, the lower part of the neck and both femoral regions. Dr. Holmes informed us that the exposure time at each treatment was twenty minutes and that other factors in the procedure were as follows: The roentgen rays were produced by a current with 200 kilovolts. The rays were filtered through 0.5 mm. of copper and 4.0 mm. of aluminum. The target-skin distance was 175 cm.

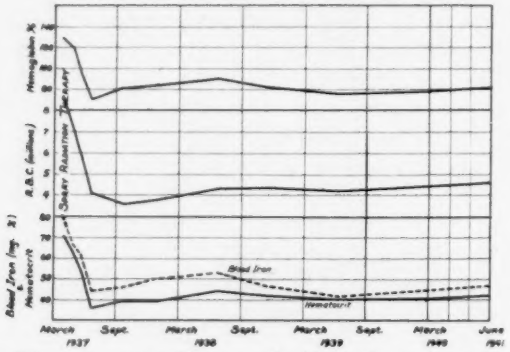

Fig. 2.—Effect of spray radiation on the blood of a patient with polycythaemia vera.

The result of this treatment was gratifying. So far as one could measure clinically, the polycythemia disappeared.

The blood count returned to normal in every way and remained normal or even subnormal for the rest of the patient's life. His general condition improved remarkably. He gained 16 pounds (7.3 Kg.) in weight, carried on a heavy practice without complaint, felt normally well and claimed that his only physical limitation was due to what he termed "that damned angina."

Further Details of Case.—Clearly, in reexamining the patient from time to time, it was evident that his vascular disease progressed. Each time the blood pressure was estimated, the level was far too high. He came to have a great deal of angina, relieved in part by the steady use of theophylline with ethylenediamine and glyceryl trinitrate. He had one major attack which was suggestive of coronary thrombosis. He quickly grew to look older, as do so many people with advancing vascular disease. He had one minor attack of transitory aphasia,

which made him regard his cerebral vessels with distrust. Yet on the other side of the picture, he was able to do a man's work each day; the overfull veins of the eyegrounds disappeared; the size of the spleen receded, so that it became impalpable; his headache and mental stuffiness disappeared, as did the pain in his arms and legs, and whatever signs of renal involvement there ever were, vanished. The concentration of nonprotein nitrogen in the blood remained low, and the urine never showed more than the faintest trace of albumin, with normal sediment.

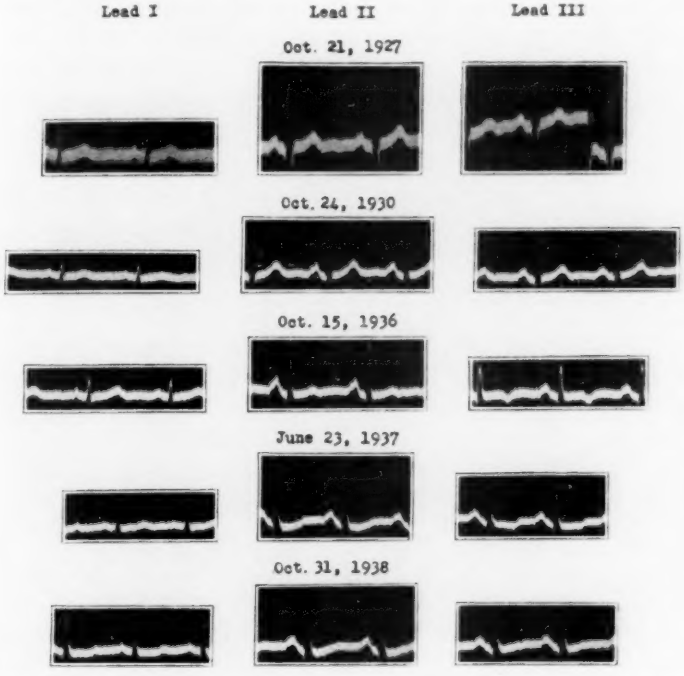

Fig. 3.—The progress of vascular disease in a patient with polycythaemia vera, as shown by serial electrocardiographic tracings. There is a gradual and progressive change in the form of the ventricular complex in all three leads.
(This comment was provided by Dr. S. A. Levine, who made the tracings.)

The patient died in his office suddenly in November 1941, four and a half years after his course of roentgen treatment was completed and just as he had finished a busy afternoon of seeing patients.

Necropsy: Macroscopic examination. The heart was slightly hypertrophied. There were two small areas of dense gray fibrous tissue apparently from old infarctions, one approximately 5 mm. in diameter near the apex of the left ventricle in the outer wall, the other about 1 cm. in diameter in the interventricular septum just beneath the mesial cusp of the aortic valve. No recent infarcts were seen. The appearance of the heart muscle was more normal than would have been expected from the condition of the coronary vessels. The

endocardium was normal except for atheromatous thickening, with some calcification of the mitral and the aortic valve base.

Both coronary vessels showed an advanced degree of atheromatous degeneration, with many calcified plaques appearing in beadlike chains along the surface vessels. The right coronary artery, beginning 1 cm. distal to its orifice, was a solid fibrous cord, with only a threadlike lumen no more than 0.25 mm. in diameter.

The aorta showed advanced arteriosclerosis throughout its entire course. This was most pronounced below the diaphragm, the abdominal aorta having several extensive atheromatous ulcers and plaques of calcification. There was no thrombosis.

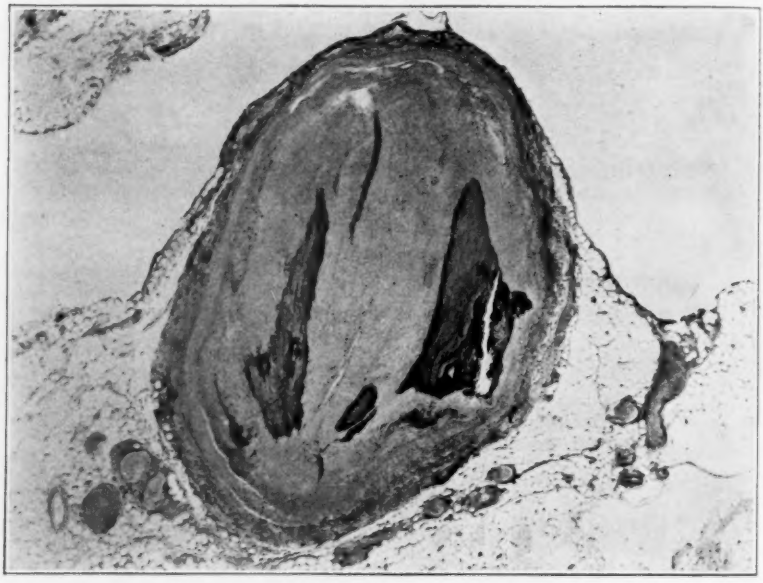

Fig. 4.—The right coronary artery (× 30). A section through its middle portion, showing complete occlusion by an old, organized thrombotic mass. There is partial calcification of the artery and no canalization of any consequence.

The vessels of the lung showed only a minimal degree of atheromatous change, and the lung tissue itself had no chronic inflammatory process, so that nothing like Ayerza's disease could account for the polycythemia. The mediastinum also was normal.

The liver was congested but otherwise showed no abnormality on gross examination.

The spleen was about twice normal size. The splenic artery was markedly sclerosed and contained many atheromatous plaques. In fact, the lumen of the vessel appeared to be only about half the normal diameter. The gross appearance of the spleen was that of congestion, although the capsule was flecked with

many minute siderotic nodules, such as frequently are seen in association with Banti's syndrome.

The kidneys were of about normal size and shape. The renal arteries presented an advanced degree of atherosclerosis, in many areas so marked as almost completely to occlude the vessels. On the other hand, the normal relation between cortex and pyramids was well preserved.

The cortex showed no gross abnormalities; the capsule stripped easily, leaving a uniformly granular surface, and the pelves and ureters were normal. The disparity between the amount of atherosclerosis in the renal arteries and the relatively normal appearance of the renal tissue was striking.

The gastrointestinal tract and the pancreas were not noteworthy.

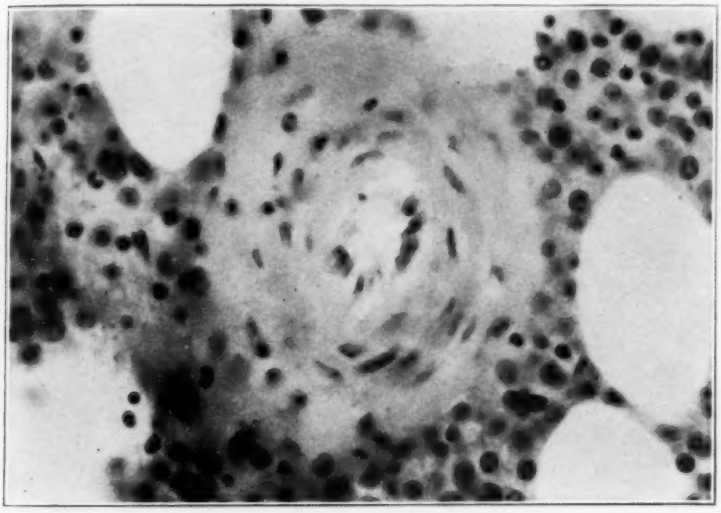

Fig. 5.—Vertebral marrow (× 400). The arteriole shown in the center is practically occluded by fibrous thickening of the media. There is marked erythroblastosis.

The sternal, vertebral and femoral bone marrow appeared normal. The femoral marrow was bright lemon yellow, fatty and did not show any recognizable islands of secondary hyperplasia.

Microscopic examination. There were striking vascular changes in all the tissues examined, particularly noteworthy in the vertebral and sternal bone marrow, the spleen, the kidney and the heart.

Through various portions of the heart advanced myocardial fibrosis was apparent. There were extensive areas in which muscle bundles had disappeared entirely and were replaced by a relative increase of the connective tissue about them. The majority of the blood vessels showed well defined fibrous thickening of the intima, and the right coronary artery and its branches were completely occluded by masses of dense, old, organized thrombotic material.

The kidneys also showed changes of vascular origin. There were areas in which the glomeruli were sclerosed, in which the tubules were atrophic or absent and in which the connective tissue was relatively increased and infiltrated with lymphocytes. The majority of the afferent arterioles were almost totally occluded by dense patches of hyalinization, in places having the appearance of necrotizing arteriolitis.

The germinal centers of the spleen were well preserved and stood out sharply but on close examination were definitely hematopoietic. Through the stroma was a moderate degree of general fibrosis, but in addition there were scattered small areas of active hematopoiesis in which both erythrocytic and leukocytic elements were present.

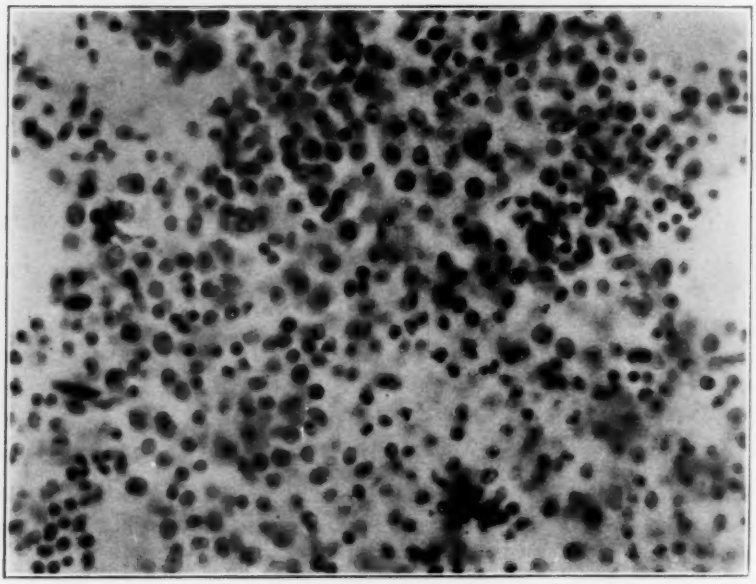

Fig. 6.—Sternal marrow (× 375). There is marked erythropoiesis.

The capsule was thickened, and in it were large numbers of hemosiderin-laden macrophages and of infiltrating lymphocytes and endothelial cells. Scattered throughout were many minute petechial hemorrhages.

The splenic arterioles tended to be fibrosed, with hyaline thickening of the intima. This change, however, was no more marked than often occurs in elderly persons with arteriosclerosis.

The bone marrow was especially interesting. The femoral marrow was not remarkable. Sections through the vertebral and the sternal marrow, however, revealed essentially the same picture. There was active erythropoiesis, not accompanied by a concomitant degree of new white cell formation. A moderate number of fat cells were present, and relatively large numbers of megakaryocytes

were visible. The arterioles and the capillaries presented well defined and unmistakable fibrous thickening.

The lungs were not remarkable except that many of the peribronchial arterioles showed fibrous thickening of the intima, often involving the inner portion of the media. The liver did not present any striking histologic abnormalities. The vessels of the adrenal glands were also involved in the general picture of vascular disease which was present; several of the smaller arterioles were occluded by atheromatous plaques with fibrosis and hyalinization of the intima and the media. Naturally, sections from the aorta showed extensive subintimal patches of atheromatous degeneration infiltrated with many fat-laden macrophages, lymphocytes and neutrophils.

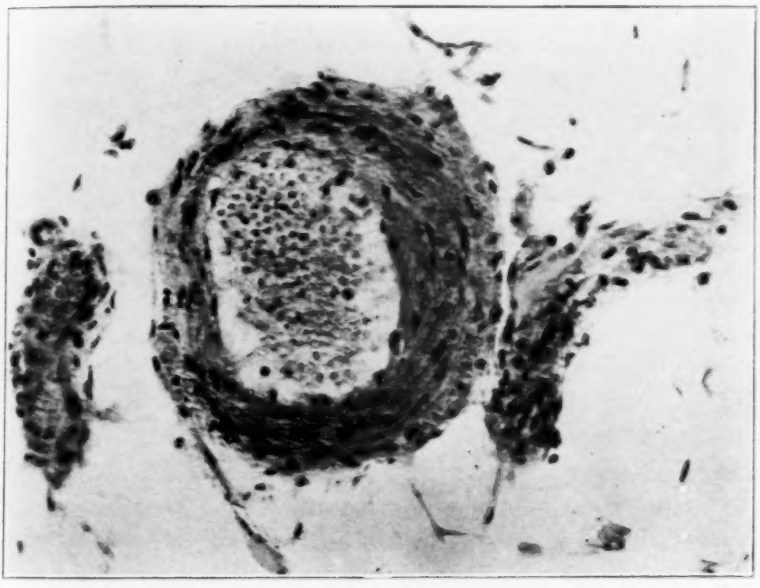

Fig. 7.—Femoral marrow (× 150). Section through the middle portion of the femur. There is no evidence of erythropoiesis, as appeared in the sternal and the vertebral marrow. The wall of the arteriole shown in the center is thickened because of fibrosis.

COMMENT

One phase of polycythaemia vera has received but little study; this concerns iron. Obviously, the vast number of red cells and the high concentration of hemoglobin utilize a great deal of this element. It has been assumed that this is obtained from deposits in the body. When our patient was polycythemic, a good share of his stored iron must have been in circulation, hence we were curious to ascertain what effect, if any, this had on the final iron content of his tissues.

Comparatively little has been acquired during the past thirty years in the way of authentic record of the iron content of human tissues. Magnus-Levy [11] in 1910 analyzed one body from this viewpoint; van Itallie in 1926, as reported by Donath,[12] and Donath himself in that year made more extensive analyses; in 1930 Horsters [13] became interested in the iron content of the organs in different forms of jaundice, reporting at the same time a few control figures from patients without jaundice, and in 1935 Sheldon,[14] in his excellent monograph on hemochromatosis, gave figures for the iron content of tissues of patients dying of this disease, appending to his tables a contrasting series of "normal control figures." These are all the available data that we could find.

There is general agreement that kidney, liver, spleen and striated muscle are the most important storehouses in which hoarding or depletion of iron becomes evident. The following tabulation is of some interest:

	Kidney	Liver	Spleen	Striated Muscle
Iron in Mg. per Cent of Dried Tissue				
Magnus-Levy, 1910, normal subjects	83	335	386	125
Horsters, 1930, "control cases"	97	345	404	...
Sheldon, 1935, "normal control figures"	39	50 to 100	140	25
Our patient	49	153	136	41
Iron in Mg. per Cent of Undried Tissue				
Donath, 1926, Chinese and native Dutch East Indians	11	21	48	...
van Itallie, 1926, European subjects	6	18	51	...
Our patient	8	42	30	...

There is a wide discrepancy in these figures. Ours are considerably lower than the ones reported by Magnus-Levy or Horsters but agree fairly well with those of Sheldon, Donath and van Itallie except as they concern liver. Our figures are directly comparable with Sheldon's, for like him we employed the technic of ashing and the method of Kennedy [15] for analysis for iron.

11. Magnus-Levy, A.: Ueber den Gehalt normaler menschlicher Organe an Chlor, Calcium, Magnesium und Eisen sowie an Wasser, Eiweiss und Fett, Biochem. Ztschr. **24**:362-380, 1910.

12. Donath, W. F.: Chemical Iron Analysis in Organs, Mededeel. v. d. dienst d. Volksgezondh. in Nederl.-Indië **3**:184-239, 1926.

13. Horsters, H.: Ueber den Eisengehalt der Organe beim Ikterus, Arch. f. exper. Path. u. Pharmakol. **152**:198-209, 1930.

14. Sheldon, J. H.: Haemochromatosis, London, Oxford University Press, 1935, pp. 205-219.

15. Kennedy, R. P.: The Quantitative Determination of Iron in Tissues, J. Biol. Chem. **74**:385-391 (Aug.) 1927.

Sheldon said of liver:

> The normal standard is somewhat variable, but the average normal dry percentage is usually between 0.05 per cent. and 0.1 per cent., which implies an increase in haemochromatosis of some 40 times the normal.

One may conclude, therefore, that the liver iron of our patient may have been higher than normal, perhaps from chronic passive congestion, but it was by no means strikingly so. Otherwise, there was nothing in our data to suggest that excess storage of iron in any ordinary area or unusual withdrawal of iron from it played any part in the clinical picture which we observed.

This case raises three interesting questions: Why did the patient become polycythemic? What was the exact effect of the irradiation? Why did he have so long a remission?

As has been mentioned, the thought that vascular disease was the underlying lesion in this instance has considerable appeal. It is easy to imagine that vascular disease, when so general as it was here and involving as it did small vessels of the bone marrow, might cause thereby a chronic anoxemia of the red cell–forming apparatus. A few years ago Monge [16] pointed out the great similarity between the erythremic type of high altitude disease and polycythaemia vera, the chief difference being that erythremia due to high altitude subsides promptly when the patient lives at sea level. As a theory to explain the course of our patient's illness one might postulate a vascular lesion with involvement of the bone marrow circulation which made the blood behave as though the patient, to all intents and purposes, were living at a high altitude. As the blood count fell to normal, the blood lost its excessive viscosity; the circulation in the marrow improved; perhaps a new and effective capillary circulation was able to develop to a certain extent; the patient came back to earth, so to speak, and the polycythemia disappeared.

The effect of irradiation on the blood picture is also difficult to account for. The data reported by Lawrence in his studies on the use of radioactive phosphorus in the treatment of polycythemia suggest that irradiation has a strikingly different effect on the red cells than does either phenylhydrazine or bleeding. There is abundant evidence in the studies of investigators at the Mayo Clinic [17] that phenylhydrazine is a powerful hemolytic agent. Red cells are destroyed by

16. Monge, C.: High Altitude Disease, Arch. Int. Med. **59**:32-40 (Jan.) 1937.

17. Giffin, H. Z., and Allen, E. V.: Experiments with Phenylhydrazine: I. Studies on Blood, Ann. Int. Med. **1**:655-676 (March) 1928. Allen, E. V., and Giffin, H. Z.: Experiments with Phenylhydrazine: II. Studies on Renal and Hepatic Function and Erythropoiesis, ibid. **1**:677-682 (March) 1928. Allen, E. V., and Barker, N. W.: Experiments with Phenylhydrazine: III. Pathological Anatomy, ibid. **1**:683-693 (March) 1928.

it; the nonprotein nitrogenous elements of the blood are increased temporarily after its administration; jaundice may develop, and, finally, the destroyed corpuscles are excreted, as can be shown by experiments on nitrogen excretion. Iron metabolism is so peculiarly economical, however, that iron is not lost from the body by such destruction of red cells. It may go into storage to be used over again or may be deposited in the liver, spleen or kidney. By bleeding the iron stores are actually depleted. Reimann and Breuer [18] have discussed this phase of the treatment of polycythemia most satisfactorily. Lawrence's report suggests that irradiation gets rid of red cells in some fashion without producing evidence either of blood destruction or of blood loss. How this occurs is not clear.

In our case, certainly, there was no apparent loss of blood following roentgen treatment. All that seemed to happen was a gratifying fall in hemoglobin concentration and blood count, with notable improvement in the patient's general sense of well-being. It is obvious, however, that our data are not sufficiently complete to exclude a slow hemolysis. That this probably occurred is suggested by the fact that eleven days after the treatment was completed, the serum iron concentration was 3.6 mg. per hundred cubic centimeters.

The true significance of our pathologic data is difficult to interpret with perfect assurance. In the literature are reported many cases of polycythaemia vera in which by one means or another the picture of the disease has been erased for varying lengths of time. The usual story is that the picture redevelops eventually. One always can claim, therefore, that our patient died of heart failure before a remission of polycythemia ended, which was either induced or spontaneous. In favor of this is the fact that histologic examination of the vertebral and the sternal marrow and of the spleen showed a degree of hematopoietic activity not ordinarily encountered in persons with chronic heart failure. On the other hand, the essential lesion, both clinical and pathologic, was that of generalized vascular disease.

Is it possible that originally polycythemia developed in our patient from abnormalities in the circulation of the bone marrow and that irradiation reduced the blood count, hemoglobin concentration and blood viscosity to normal, thereby making way for a better flow of blood, and is it possible that a permanently improved bone marrow circulation thus was stimulated, finally making our case one of healed or inactive polycythaemia vera? We incline to interpret our data in this manner and hope that this case offers promise that in certain instances polycythaemia vera may become so inactive that to all intents

18. Reimann, F., and Breuer, A.: Die Aderlassbehandlung der Erythrämie, Ztschr. f. klin. Med. **128**:238-259, 1935.

and purposes the patient recovers. Other patients with known polycythemia in a state of clinical remission must be studied by the pathologist in order to throw more light on what the exact lesion in different types of polycythaemia vera may be and what the true condition really is.

On May 7, 1892, Vaquex [19] presented a paper before the Parisian Society of Biologists entitled, *"Sur une forme spéciale de cyanose s'accompagnant d'hyperglobulie excessive et persistante."* Its purpose was to call attention to the fact that there might be encountered in the clinic a peculiar group of patients without evidence of heart disease who appeared thoroughly cyanosed, who complained of a variety of

SUR UNE FORME SPÉCIALE
DE CYANOSE S'ACCOMPAGNANT D'HYPERGLOBULIE EXCESSIVE ET PERSISTANTE,

par M H. VAQUEZ.

Les recherches poursuivies dans ces dernières années sur les modifications du sang et dans les maladies ont porté presque exclusivement sur les altérations globulaires, les changements d'aspect des éléments figurés, la constitution du sérum, etc.; on a noté les différentes conditions capables de provoquer la diminution du nombre des globules rouges ou l'augmentation de celui des globules blancs, mais c'est à peine si l'on a signalé la possibilité de l'hyperglobulie.

Il y a cependant des cas où le nombre des globules rouges peut être considérablement augmenté et, du fait de cette augmentation, il résulte un ensemble de symptômes qu'il est intéressant d'étudier.

Au point de vue physiologique, les auteurs ont déjà noté que le nombre des globules rouges pouvait se trouver sensiblement accru à la suite des repas (1), et par le séjour dans les hautes altitudes. M. Viault (2) a montré que dans ces conditions le nombre des globules rouges pouvait, déjà au bout de quelques jours, et suivant les personnes, atteindre 7,300,000 à 7,900,000.

Fig. 8.—The commencement of present knowledge of polycythaemia vera.

ill defined symptoms and who presented characteristically an enlarged spleen and a red cell count and hemoglobin concentration much higher than normal. The cause of this syndrome was undetermined. Major [20] has regarded this paper as affording a classic description of a rare disease, and it does, indeed, describe clearly for the first time what has come to be known as polycythaemia vera.

19. Vaquez, H.: Sur une forme spéciale de cyanose s'accompagnant d'hyperglobulie excessive et persistante, Compt. rend. Soc. de biol. **4**:384-388 (May 7) 1892.

20. Major, R. H.: Classic Descriptions of Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932, pp. 455-465.

It seems curious, as one looks backward, to realize how little attention was paid to this publication. Osler [21] was the first American writer to acknowledge it and then not until 1903. In this year he published a paper, "Chronic Cyanosis with Polycythaemia and Enlarged Spleen: A New Clinical Entity," and thereby aroused an interest in that group of patients first noted by Vaquez which has persisted ever since.

The literature on polycythaemia vera has grown to large proportions. It is a peculiar literature, for it reflects new currents of medical progress as they have developed, without, however, adding much to a clear understanding of what polycythaemia vera really is. Fifty years ago Vaquez expressed the hope that one day some one might be able fully to account for that form of polycythemia which he described and the cause of which he was at a loss to explain. Modern clinicians, with the many advantages which they have at hand, still are challenged to give a final answer to this question.

319 Longwood Avenue.

80 East Concord Street.

750 Harrison Avenue.

21. Osler, W.: Chronic Cyanosis with Polycythæmia and Enlarged Spleen: A New Clinical Entity, Am. J. M. Sc. **126**:187-201 (Aug.) 1903.

CLEARANCE OF DIODRAST, PHENOLSULFONPHTHALEIN AND INULIN IN HYPERTENSION AND IN NEPHRITIS

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ST. LOUIS

Despite Smith's [1] demonstration that under proper conditions the plasma clearance of diodrast closely approximates renal plasma flow, the detection of renal ischemia in human beings is evidently not a simple matter. Its existence in patients with hypertensive disorders has been claimed by some authors [2] and denied by others.[3] This report

From the Departments of Medicine and Physiology, Washington University School of Medicine, and the St. Louis City Hospital. This study was aided by grants from the Smith, Kline and French Laboratories, Philadelphia (T. F.), and the Commonwealth Fund (H. L. W.).

1. Smith, H. W.; Goldring, W., and Chasis, H.: The Measurement of the Tubular Excretory Mass, Effective Blood Flow and Filtration Rate in the Normal Human Kidney, J. Clin. Investigation **17**:263, 1938.

2. (*a*) Smith, H. W.: Studies on the Physiology of the Kidney, Porter Lecture Series, no. 9, Lawrence, University of Kansas, University Extension Division, 1939. (*b*) Goldring, W.; Chasis, H.; Ranges, H. A., and Smith, H. W.: Effective Renal Blood Flow and Functional Excretory Mass in Essential Hypertension, J. Clin. Investigation **17**:505, 1938. (*c*) Smith, H. W.; Goldring, W.; Chasis, H., and Ranges, H. A.: Observations on the Effective Renal Blood Flow and Functional Excretory Mass in Man, with Special Reference to Essential Hypertension, Am. J. Physiol. **123**:189, 1938. (*d*) Chasis, H., and Redish, J.: Unilateral Renal Function in Essential Hypertension, J. Clin. Investigation **20**:442, 1941. (*e*) Corcoran, A. C., and Page, I. H.: Renal Function in Late Toxemia of Pregnancy, Am. J. M. Sc. **201**:385, 1941. (*f*) Friedman, M.; Selzer, A., and Rosenblum, H.: The Renal Blood Flow in Coarctation of the Aorta, J. Clin. Investigation **20**:107, 1941. (*g*) The Renal Blood Flow in Hypertension, J. A. M. A. **117**:92 (July 12) 1941.

3. (*a*) Chesley, L. C.; Connell, E. J.; Chesley, E. R.; Katz, J. D., and Glissen, C. S.: The Diodrast Clearance and Renal Blood Flow in Toxemias of Pregnancy, J. Clin. Investigation **19**:219, 1940. (*b*) Chesley, L. C., and Chesley, E. R.: Renal Blood Flow in Women with Hypertension and Renal Impairment, ibid. **19**:475, 1940. (*c*) Chesley, L. C.: The Question of Glomerular Damage Following Toxemia of Pregnancy, Am. J. Obst. & Gynec. **42**:229, 1941. (*d*) Welsh, C. A.; Willen, I., and Taylor, H. C., Jr.: Renal Blood Flow, Filtration Rate and Tubular Excretory Mass in Patients with Specific Toxemia of Pregnancy, J. Clin. Investigation **20**: 438, 1941.

on a small series of subjects with normal and with diseased kidneys attempts to reconcile these divergent statements.

Since no ratios for diodrast extraction based on human material have been published, the validity of the clearance method of measuring renal blood flow clinically is not conclusively established. Indirect evidence, however, suggests that the agreement between actual blood flow and estimated blood flow is even closer in human beings than in dogs.[4] There being no reason to doubt that the plasma clearance of inulin is an accurate measure of the rate of glomerular filtration,[5] the ratio of plasma inulin clearance to plasma diodrast clearance can represent the fraction of plasma water which traverses Bowman's membrane. Hence, such other factors as membrane permeability and plasma oncotic pressure remaining constant, this ratio can vary directly with intraglomerular hydrostatic pressure and may be used to detect changes in the relative calibers of the afferent and the efferent glomerular arterioles.[6]

There is no doubt, for example, that the clearances of inulin and diodrast are capable of depicting the circulatory changes induced in the kidney by various pharmacologic agents. Smith's [6] pioneer studies in this field dramatically demonstrated the profound effects of various drugs on renal hemodynamics, and this method has been used by other investigators.[7] The conclusion seems logical that an agent which depresses diodrast clearance without appreciably affecting the simultaneous inulin clearance is selectively constricting the efferent glomerular arteriole, because preglomerular constriction can only diminish filtration pressure and, consequently, the inulin clearance. Under such circumstances the ratio between inulin clearance and diodrast clearance is clearly entitled to be referred to as the "filtration fraction." [2a]

In morbid states, however, in which the integrity of tubule function may properly be questioned, the problem is less simple. It is apparent, for example, that any factor which impairs the capacity of the renal

4. White, H. L.; Findley, T., and Edwards, J. C.: Interpretation of Diodrast Clearances in Man, Proc. Soc. Exper. Biol. & Med. **43**:11, 1940.

5. Smith, W. W.; Finkelstein, N., and Smith, H. W.: Renal Excretion of the Hexitols (Sorbitol, Mannitol and Dulcitol) and Their Derivatives (Sorbitan, Iso-Mannide and Sorbide) and Endogenous Creatine-Like Chromogen in Dog and Man, J. Biol. Chem. **135**:231, 1940.

6. Chasis, H.; Ranges, H. A.; Goldring, W., and Smith, H. W.: The Control of Renal Blood Flow and Glomerular Filtration in Normal Man, J. Clin. Investigation **17**:683, 1938.

7. (*a*) Corcoran, A. C.; Kohlstaedt, K. G., and Page, I. H.: Changes of Arterial Blood Pressure and Renal Hemodynamics by Injection of Angiotonin in Human Beings, Proc. Soc. Exper. Biol. & Med. **46**:244, 1941. (*b*) Black, D. A. K.; Powell, J. F., and Smith, A. F.: Inulin and Perabrodil Clearance After Alimentary Hemorrhage in Man, J. Physiol. **99**:344, 1941.

tubules to secrete diodrast will also elevate the ratio of inulin clearance to diodrast clearance, even though the glomerular circulation remains unaltered. By itself, therefore, the ratio is incapable of describing the circulation pattern in diseased kidneys, several recent reports to the contrary.[8] We believe that in terms of renal blood flow the ratio is meaningless unless supported by a quantitative assay of the secretory power of the tubules and agree with Smith and associates[9] that both aspects of renal function (diodrast clearance and tubular excretion of diodrast) must be measured before one is entitled to say that the blood flow per unit of tubular tissue is or is not abnormal.

A confirmation of Smith's experience with epinephrine[2a] illustrates the importance of this concept (table). By using the technic described

Effect of Epinephrine on Renal Function in a Normal Subject

	2/6/40					2/10/40				
No. of Clearance Period	Plasma Concentration, Mg./100 Cc.		Plasma Clearance Cc./Min./1.73 Sq. Meters		Inulin Clearance/ Diodrast Clearance	Plasma Concentration, Mg./100 Cc.		Plasma Inulin Clearance, Cc./ Min./ 1.73 Sq. Meters	Tubular Secretion of Diodrast, Mg./ Min./1.73 Sq. Meters	Blood Pressure, Mm. Hg
	Diodrast	Inulin	Diodrast	Inulin		Diodrast	Inulin			
1	1.35	57	511	96	0.188	66.0	54	91	31.6	105/65
2	1.27	52	510	90	0.194	63.8	49	94	31.9	108/68
3	1.21	49	416	92	0.221	62.7	47	100	31.1	108/70
1 Cc. of Solution of Epinephrine Hydrochloride (1:1,000) Administered Subcutaneously										
4	1.2	49	430	100	0.223	62.5	47	71	22.7	112/65
5	1.3	49	332	93	0.28	62.4	47	84	31.8	142/48
6	1.45	49	282	91	0.323	62.0	48	80	34.7	148/52
7	1.53	48	220	95	0.432	61.4	48	83	36.6	144/52
8	1.4	46	226	95	0.42	60.4	49	82	39.9	134/55

in the next section, consecutive fifteen minute clearance periods were obtained, the first three serving as controls. Under the established conditions epinephrine evidently reduced renal plasma flow by about 50 per cent but had no effect on the ability of the tubules to secrete iodine. In fact, the tubular secretion of diodrast actually increased, a phenomenon also noted by Smith and interpreted by him as a possible indication that new blood channels in peritubular tissue had been forced open. Now if epinephrine had reduced the tubular secretion of diodrast, it would clearly have been impossible to attribute the increased ratio between inulin clearance and diodrast clearance to ischemia alone, since diminished extractions of diodrast must also be accounted for.

8. Black, Powell and Smith.[7b] Footnote *2 e, f* and *g*. Footnote *3 a, b* and *c*.

9. Goldring, W.; Chasis, H.; Ranges, H. A., and Smith, H. W.: Relations of Effective Renal Blood Flow and Glomerular Filtration Rate to Tubular Excretory Mass in Normal Man, J. Clin. Investigation **19**:739, 1940.

As an expression of the rate of plasma flow per unit of tubular excretory mass it is convenient to adopt Smith's formula, the ratio between plasma diodrast clearance and tubular excretory mass.[10] If this is applied to data recorded before the administration of epinephrine, a value of $\frac{479}{31.5} = 15$ is obtained; at the height of the pressor response to epinephrine the figure drops to $\frac{220}{36.6} = 6$. Had the low diodrast clearance in period 7, for example, been due to diminished extraction rather than to ischemia the ratio would have remained unchanged. Our observations are inadequate to permit a statistical evaluation of normal limits, but they do show that hypertension frequently exists without demonstrable renal ischemia.

We are reporting results obtained on a relatively small series of subjects with essential hypertension and with other varieties of renal disease. We have subdivided these subjects into three clinical groups: (*a*) those with presumably uncomplicated essential hypertension; (*b*) those in whom hypertension is associated with presumptive clinical evidence of tubular damage (arteriosclerosis, retinitis, known duration of disease, diminished urea clearance, glomerulonephritis, nephrotic syndrome, congestive heart failure, abnormal urinary sediment, etc.), and (*c*) those with renal disease but normal blood pressure. We feel that this admittedly arbitrary arrangement has facilitated interpretation of the data.

METHODS

On the morning of the test, food, medication and tobacco were withheld from all subjects. Adequate hydration and diuresis were assured by the oral administration of at least 1 liter of water about an hour before the first collection of urine and by the subsequent ingestion of 200 cc. every half hour. In every case the body temperature was within 1 degree of 37 C. (98.6 F.). Urine was collected through an indwelling catheter and the bladder washed three to five times with 20 cc. portions of physiologic solution of sodium chloride. In order to diminish emotional factors the urethra was always anesthetized, and in many cases venipuncture was also done with the area under local anesthesia. Blood pressure was recorded at frequent intervals.

Before each infusion a sample of blood was obtained, part of which served as an inulin blank: to the plasma of another portion a known amount of diodrast was added, and the percentage of iodine recoverable in trichloroacetic acid filtrate was determined. All samples of blood were treated with heparin, and the plasma was separated as soon as possible. Determinations of diodrast iodine were done either by the original[11] or by the modified[12] method of White and Rolf. Inulin

10. Smith, H. W.; Chasis, H.; Goldring, W., and Ranges, H. A.: Glomerular Dynamics in the Normal Human Kidney, J. Clin. Investigation **19**:751, 1940.

11. White, H. L., and Rolf, D.: A Rapid Micro-Method for Determining Diodrast and Inorganic Iodide Iodine in Blood and Urine, Proc. Soc. Exper. Biol. & Med. **43**:1, 1940.

12. White, H. L., and Rolf, D.: Modified Method for Determination of Certain Organic Iodine Compounds, Inorganic Iodide in Plasma and Urine, Proc. Soc. Exper. Biol. & Med. **45**:433, 1940.

was determined by a slight modification of the method of Corcoran and Page.[13] Phenolsulfonphthalein also was estimated by the method of Corcoran and Page.[14] Urea clearance was determined by the hypobromite method without permutit (a hydrated sodium aluminum silicate).[15]

The actual procedure was essentially that devised by Smith and associates.[9] Infusions were delivered from a gravity bottle to which was attached a small calibrated side arm tube; this permitted a quick and accurate check on the rate of flow, changes in which were governed by a tunnel clamp on the outlet tubing. For determination of renal blood flow the following plasma concentrations were desired per hundred cubic centimeters: diodrast iodine, 1 to 5 mg.; inulin, 8 to 15 mg. and phenolsulfonphthalein, 0.5 to 1.0 mg. In the average adult these were usually achieved by (*a*) a priming solution made by adding 1.5 cc. of diodrast [16] and 0.5 cc. of 10 per cent phenolsulfonphthalein to the contents of a 50 cc. ampule of 10 per cent inulin,[17] the intravenous injection of which occupied five minutes, or (*b*) a sustaining solution consisting of 1 per cent diodrast, 0.5 per cent inulin and 0.8 per cent phenolsulfonphthalein in physiologic solution of sodium chloride delivered at the rate of 4 cc. per minute. In case of manifest renal insufficiency the infusion rate was reduced to 1 or 2 cc. per minute. To insure equilibration the infusion was continued for twenty minutes before the first collection of urine was begun. At that time the first sample of blood was drawn, the urine in the bladder was discarded and consecutive ten to twenty minute clearance periods were obtained in the usual way. Midperiod plasma concentrations of diodrast iodine, phenolsulfonphthalein and inulin were found by interpolation from at least three actual analyses, all done in duplicate. The flow of urine was such that all urea clearances were maximum.

The conditions for determining the tubular secretion of diodrast were established by injection through a syringe of 0.3 cc. of diodrast per kilogram of body weight, the injection requiring from three to five minutes. The second sustaining fluid consisted of 10 per cent diodrast and 0.5 per cent inulin in physiologic solution of sodium chloride, the rate of flow being continued as before. This usually resulted in a concentration of 25 to 30 mg. of diodrast iodine per hundred cubic centimeters of plasma, a level well above that at which tubular saturation occurs.[18]

Hematocrit readings were obtained on every sample of blood to permit calculation of renal whole blood flow by the ratio of plasma diodrast clearance to the plasma volume in percentage. We are aware that Smith and Smith [19] reported that plasma protein binds a small amount of diodrast and thus renders it unavailable for glomer-

13. Findley, T., and White, H. L.: Measurement of Diodrast and Inulin Clearances in Man After Subcutaneous Administration, Proc. Soc. Exper. Biol. & Med. **45**:623, 1940.

14. Corcoran, A. C., and Page, I. H.: The Effects of Renin, Pitressin and Pitressin and Atropine on Renal Blood Flow and Clearance, Am. J. Physiol. **126**:354, 1939.

15. Van Slyke, D. D.; Page, I. H.; Hiller, A., and Kirk, E.: Comparison of Urea Clearances Calculated from the Excretion of Urea, of Plus Ammonia, and of Nitrogen Determinable by Hypobromite, J. Clin. Investigation **14**:901, 1935.

16. The diodrast was supplied by the Winthrop Chemical Co., Inc., New York.

17. The inulin was supplied by Standard Products Co., Woodworth, Wis.

18. Smith, Goldring and Chasis.[1] White, Findley and Edwards.[4]

19. Smith, W. W., and Smith, H. W.: Protein Binding of Phenol Red, Diodrast and Other Substances in Plasma, J. Biol. Chem. **124**:107, 1938.

ular filtration, whereas Elsom, Bott and Shiels [20] considered that all plasma diodrast was free; in calculating the glomerular excretion of diodrast we have used the Smith nomogram,[19] but we realize that even at the high plasma concentrations necessary for determination of the tubular excretory mass the difference is almost negligible. When the concentration of albumin in the plasma was found by actual analysis to be less than 4 Gm. per hundred cubic centimeters, calculations were based on the observed value; otherwise a uniform value of 4 Gm. was arbitrarily used.

RESULTS ON NORMAL SUBJECTS

We have examined 17 men, all healthy medical students or laboratory assistants less than 40 years of age, with maximal urea clearances greater than 50 cc. per minute per 1.73 square meters. Data were obtained on every subject for at least three consecutive periods. All values are referred to a surface area of 1.73 square meters.

Plasma Diodrast Clearance.—The average diodrast clearance for one hundred periods in 17 subjects is 544 cc. per minute, with extremes of 402 and 785 cc. This is a little higher than a previous estimate by some of us [4] of 497 cc. per minute in 11 subjects. It agrees well with Chesley's latest report [8c] of 567 cc. in normal women and with the value 537 cc. obtained by Black, Powell and Smith [7b] presumably on mixed subjects. It is still appreciably lower for some reason than the latest estimate by Smith and associates [9] of 688 cc. in normal men.

Whole Blood Flow.—From the same material our average value for whole blood flow is 1,010 cc. per minute, with extremes of 821 and 1,380 cc., as compared with Smith's value of 1,189 cc. per minute.

Plasma Inulin Clearance.—For ninety-nine periods in 12 subjects the average value for inulin clearance is 117 cc. per minute, with extremes of 71 and 173 cc.

Ratio of Plasma Inulin Clearance to Plasma Diodrast Clearance.—As determined through forty-one periods in 11 subjects the average value for this ratio is 0.205, with extremes of 0.138 and 0.261.

Tubular Secretion of Diodrast.—For forty-seven periods in 9 subjects the average rate of tubular secretion of diodrast iodine is 40.1 mg. per minute, with extremes of 35 and 47.9 mg. This is also appreciably lower than the value of 53.3 mg. per minute recently reported by Smith and associates.[9] In every instance diodrast was presented to the tubules at a rate (renal plasma flow × plasma diodrast [milligrams per cubic centimeter] — glomerular excretion of diodrast [milligrams per minute]) at least 30 per cent in excess of the rate of secretion of iodine by the tubules.

20. Elsom, K. A.; Bott, P. A., and Shiels, E. H.: On the Excretion of Skiodan, Diodrast and Hippuran by the Dog, Am. J. Physiol. **115**:548, 1936.

Ratio of Plasma Diodrast Clearance to Tubular Secretion of Diodrast.—With a numerator obtained on 17 subjects and a denominator obtained on 9 subjects the average is 13.56, as compared with Smith's reported value of 13.6.

Ratio of Plasma Inulin Clearance to Tubular Secretion of Diodrast.—On the basis of gross averages from the aforementioned data the figure is 2.91 (Smith, 2.57).

Plasma Phenolsulfonphthalein Clearance.—Our experience with this substance is too limited to justify much comment, since we have used it on only 14 subjects, 12 of whom were abnormal. Its use was abandoned because it seemed to us to offer little additional information. We have not corrected our diodrast clearances for possible depression due to interference of phenolsulfonphthalein because in every instance the concentration of this substance in the plasma was less than 1 mg. per hundred cubic centimeters.

In 2 normal men the average plasma clearance of phenolsulfonphthalein in thirteen periods was 295 cc. per minute, with extremes of 265 and 354 cc. This is again lower than the mean value of 394 cc. obtained by Smith and associates on a much larger series.[1] The average value for the ratio of plasma phenolsulfonphthalein clearance to plasma diodrast clearance is 0.626.

Tubular Secretion of Phenolsulfonphthalein.—We have determined this on only 1 normal subject for obvious reasons. Tubular saturation occurred at a plasma concentration of about 15 mg. per hundred cubic centimeters, and the maximal rate of tubular secretion during four periods averaged 19.4 mg. per minute. Smith and associates [1] reported a rate of 35.8 mg. per minute in 1 case.

Since the ratio between plasma phenolsulfonphthalein clearance and plasma diodrast clearance in our small series of hypertensive subjects appeared to offer little information of value, no further reference to phenolsulfonphthalein will be made.

RESULTS ON ABNORMAL SUBJECTS

Our data on 28 patients with miscellaneous renal lesions are presented in chart 1. In order to facilitate comparison we use essentially the same graphic method employed by Smith,[2a] wherein points are arranged semilogarithmically along arbitrarily placed slanting lines. It should be particularly noticed that the values for tubular secretion of diodrast are so arranged that they fall exactly on the line; the points which represent simultaneous diodrast and inulin clearances and ratios of inulin clearance to diodrast clearance are easily found by projecting a vertical line through the point for tubular secretion of diodrast.

The open circles represent 12 subjects with presumably uncomplicated essential hypertension; i. e., they are all less than 50 years of age, they have normal urea clearances and urinary sediments and parenchymal damage is minimal so far as one is able to predict from the appearance of the eyegrounds, the absence of cardiac involvement, etc. These are the subjects in whom it is reasonable to suppose that any depression in diodrast clearance is apt to represent diminished blood flow rather than tubular damage.

The solid circles represent 12 subjects in whom hypertension is accompanied by evidence of organic renal disease. Three had chronic glomerulonephritis; 4 had cardiac involvement with mild congestive

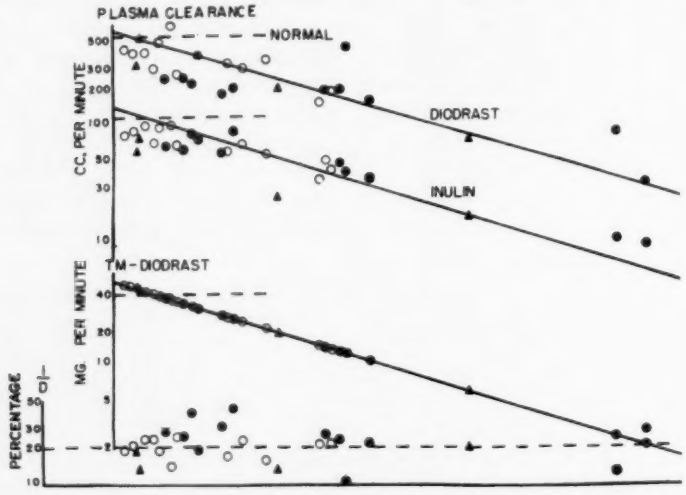

Chart 1.—Relation of tubular secretion of diodrast *(TM-Diodrast)* to diodrast clearance, inulin clearance and the ratio $(\frac{I}{D})$ of these two clearances to each other (see text). The horizontal lines indicate our normal averages; the open circles, subjects with uncomplicated hypertension; the solid circles, patients with advanced hypertension, and the triangles, patients with renal disease and normal blood pressure. If all values were displaced proportionally to tubular secretion of diodrast, they would fall on their respective slanting lines.

heart failure; 3 were more than 60 years of age and had marked arteriosclerosis with subnormal urea clearances, and 2 had uremia and the retinal picture of malignant hypertension.

The triangles account for 4 patients with renal disease but normal blood pressure. One had marked peripheral arteriosclerosis and slight proteinuria; 1 had syphilitic nephrosis, from which he recovered; another had chronic glomerulonephritis of many years' duration and a biliary

fistula, and the fourth had severe congestive heart failure with albuminuria, azotemia and jaundice, from which he also recovered.

Because of insufficient data we are unable to define statistically the limits of normal, but it is apparent that at least 7 of the 12 subjects with uncomplicated hypertension have values for tubular secretion of diodrast so close to our normal average that we are forced to assume that tubular function, as measured by the capacity for diodrast secretion, is intact. We must emphasize the fact that all of these patients were under continuous observation in the hospital and had sustained blood pressure readings in excess of 150 systolic and 100 diastolic.

None of these 12 subjects shows an elevated ratio of inulin clearance to diodrast clearance. Half of the plasma diodrast clearances fall somewhat below the predicted level but not in disproportion to the fall in corresponding inulin clearance. This is in contrast to the results obtained on 12 subjects with advanced hypertension, about half of whom exhibited ratios higher than our normal average. It is in this group that interpretation of data becomes difficult. A few deductions seem justifiable. Proportionate reductions in the clearance of diodrast and inulin and in tubular secretion of diodrast do not produce changes in either the ratio of inulin clearance to diodrast clearance or the ratio of diodrast clearance to tubular secretion of diodrast and indicate simply the presence of small kidneys; in this category we place the remaining 5 subjects with uncomplicated hypertension. Spasm of the efferent glomerular arterioles would, as in the experiments with epinephrine, so reduce diodrast clearance as to increase the ratio of inulin clearance to diodrast clearance and diminish the ratio of diodrast clearance to tubular secretion of diodrast; 5 subjects with advanced hypertension appear to fall in this class, but there is no assurance that impaired renal extraction is not a factor. Indeed, there is every reason to suppose that the kidneys of patients with the stated clinical characteristics would be unable to handle diodrast loads normally. We see no way to separate these two factors clearly, but the high ratios of inulin clearance to diodrast clearance and normal values for the ratio of diodrast clearance to tubular secretion of diodrast in the 3 other subjects in this group seem best explained by assuming that impaired tubular extraction is more important than arteriolar spasm as a cause of diminished excretion of diodrast.

Among the 4 normotensive patients there are 2 with normal and 2 with subnormal ratios of inulin clearance to diodrast clearance. Of the 2 subjects with normal values the one in whom the tubular secretion of diodrast iodine is 6 mg. per minute had severe congestive heart failure and the other (tubular secretion of diodrast iodine, 42 mg. per minute) was well except for senile arteriosclerosis and slight proteinuria: in neither patient is there reason to postulate selective damage to either

glomeruli or tubules. Of the 2 subjects with low ratios between inulin clearance and diodrast clearance, 1 had nephrosis and intense proteinuria and the other had chronic glomerulonephritis; in both altered membrane permeability may have retarded the rate of filtration.

In chart 2 the ratios between inulin clearance and diodrast clearance are plotted against the ratios of diodrast clearance to tubular secretion of diodrast in an effort to detect any relation between the so-called "filtration fraction" and the degree of renal ischemia. In general, there appears to be an inverse relation, but again only half of the 24 patients

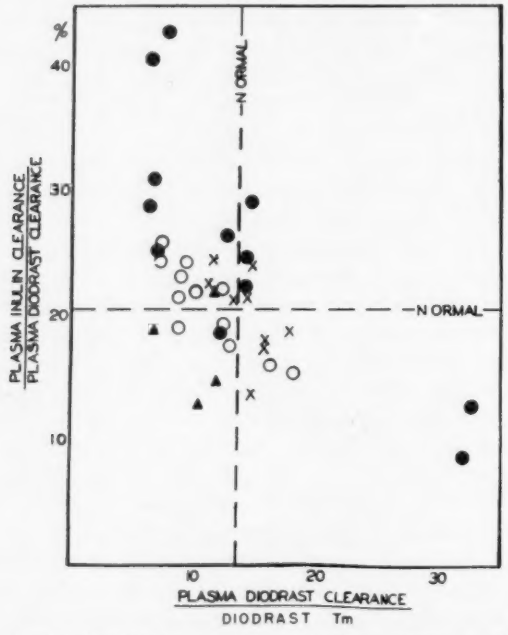

Chart 2.—Relation between the ratio of inulin clearance to diodrast clearance and renal ischemia (see text). The broken lines indicate our normal averages, and *X* signifies the normal subjects. For the significance of the other symbols see chart 1. *Diodrast Tm* sginifies tubular secretion of diodrast.

with hypertension have a ratio of diodrast clearance to tubular secretion of diodrast of less than 10, our lowest normal value. Of the 6 patients who exhibit both ischemia and a high ratio of inulin clearance to diodrast clearance, only 1 falls in the uncomplicated group. Seven of the 8 in whom this ratio exceeds 0.25 have advanced renal disease. The 4 whose ratios are less than 0.15 all have primary glomerular

disease, though only 2 of them also have hypertension, and these 2 are the only ones of the entire series whose conditions plainly fall in the zone of relative hyperemia.

COMMENT

This failure to find consistently abnormal renal circulation patterns in subjects with essential hypertension is at variance with the reports of the originators of the method; we are reluctant to draw dogmatic conclusions, particularly since our material is so limited. The mere fact, however, that even this small experience has disclosed a high percentage of patients with essential hypertension with normal clearance and normal tubular secretion of diodrast appears to lend support to the conclusion reached by others from studies on nephritis and the toxemias of pregnancy that demonstrable renal ischemia is not a constant factor in the genesis of high blood pressure and to the recent perfusion studies of Cox and Dock.[21] This is not to say, of course, that no disturbance in renal blood flow exists in these conditions; the experimental studies of Kohlstaedt and Page [22] have shown that hypertension may depend primarily on diminution of pulse pressure within the kidney rather than on an absolute reduction in total blood flow. If one considers also the well known difficulties encountered in demonstrating renal ischemia even in animals the renal arteries of which are mechanically occluded,[23] it may be that too much is being asked of the clearance method.

We do not think we have been too rigid in selecting our subjects with uncomplicated hypertension, for in every instance the diagnosis was first made by a member of the regular house staff of the hospital. We also wish to point out that the selection of the subjects with advanced or with complicated hypertension was made clinically and was not arbitrarily based on the magnitude of the ratio of inulin clearance to diodrast clearance. Yet the correlation seems clear, and we are inclined to attribute disproportionate reduction of diodrast clearance to impaired tubular extraction of diodrast rather than to increased intraglomerular pressure dependent on efferent arterial spasm. This, however, is a matter of probability rather than of demonstrated fact.

As for glomerulonephritis, we have complete data on only 4 subjects, in all of whom the condition is chronic. There is marked individual

21. Cox, A. J., Jr., and Dock, W.: The Capacity of the Renal Vascular Bed in Hypertension, J. Exper. Med. **74**:167, 1941.

22. Kohlstaedt, K. G., and Page, L. H.: Production of Renin by Constricting the Renal Artery of an Isolated Kidney Perfused with Blood, Proc. Soc. Exper. Biol. & Med. **43**:136, 1940.

23. Page, I. H.: Newer Aspects of Experimental Hypertension in Blood, Heart and Circulation: Symposium, Publication 13, American Association for the Advancement of Science, 1940, p. 239.

variation, of course, but all showed low ratios between inulin clearance and diodrast clearance, none had subnormal ratios between diodrast clearance and tubular secretion of diodrast and 2 of those with more advanced glomerulonephritis had conditions definitely in the hyperemia zone. The interpretation of these data is clouded by the theoretic possibilities of aglomerular tubules, "impotent" tubules and arteriovenous shunts, and we prefer simply to record the data.

CONCLUSIONS

Values for renal blood flow, glomerular filtration rate and tubular secretion of diodrast are reported on a series of normal subjects and patients with essential hypertension, glomerulonephritis and other types of renal disease.

Plasma clearances of diodrast and inulin, even when interpreted in the light of tubular secretion of diodrast, indicate absence of renal ischemia in a high proportion of subjects with uncomplicated essential hypertension.

Under controlled conditions the ratio between inulin clearance and diodrast clearance can represent the "filtration fraction," but high ratios in subjects with hypertension probably result from diminished diodrast extraction rather than from increased filtration pressure.

NOTE.—Since this manuscript was completed, more reports by Smith and his co-workers have appeared.[24] Our findings appear to be in general agreement, although these authors would evidently exclude from consideration any subject who has a high ratio of inulin clearance to diodrast clearance but a normal ratio of diodrast clearance to tubular secretion of diodrast on the grounds that "impotent nephrons will produce a vicarious hyperemia in such functional tissue as may be perfused by the vestigial vascular channels related to the now defunct tissue."[24b] It may be that the conversion of isolated tubules into "passive conduits" is common in Bright's disease, but we have preferred to regard diminished diodrast extraction as a consequence of diffuse parenchymal degeneration. However that may be, its existence makes detection of coexisting renal ischemia by the clearance method difficult or impossible, since blood from the renal veins is unobtainable in human beings. These investigators[24b] have, moreover, reported on 3 hypertensive subjects with normal clearance and normal values for the tubular secretion of diodrast. If these are added to our subjects with uncompli-

24. (*a*) Smith, H. W.: Note on the Interpretation of Clearance Methods in the Diseased Kidney, J. Clin. Investigation **20**:631, 1941. (*b*) Goldring, W.; Chasis, H.; Ranges, H. A., and Smith, H. W.: Effective Renal Blood Flow in Subjects with Essential Hypertension, ibid. **20**:637, 1941. (*c*) Chasis, H., and Redish, J.: Effective Renal Blood Flow in the Separate Kidneys of Subjects with Essential Hypertension, ibid. **20**:655, 1941.

cated hypertension in whom both the ratio of inulin clearance to diodrast clearance and the ratio of diodrast clearance to tubular secretion of diodrast are normal, it appears difficult to believe that renal ischemia is a constant feature in this disorder. Although our absolute values for diodrast clearance and tubular secretion of diodrast are, for some unknown reason, consistently lower than those reported by Smith and associates, it should again be noted that our normal ratios between diodrast clearance and tubular secretion of diodrast are practically identical with theirs.

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CRITICAL STATISTICAL ANALYSIS OF DATA ON RENAL FUNCTION IN GROUPED SUBJECTS WITH ESSENTIAL HYPERTENSION

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We have made a statistical study of the renal function of patients with essential hypertension. The only large series of data available to us from tests of renal function are chiefly results of the Volhard, the phenolsulfonphthalein excretion and the urea clearance test. It has been shown by a number of investigators [1] that these tests do not demonstrate remarkable reductions in renal function in persons with essential hypertension. On studying the reports on which this conclusion was based, it was evident that the opinion was obtained as a result of comparing single examples of renal function in persons with essential hypertension with single examples of renal function in a normal person in an attempt to demonstrate differential diagnostic possi-

From the Cardiovascular-Renal Research Department, Santa Barbara Cottage Hospital.

1. (*a*) Leiter, L.: Renal Function in Studies from the Lasker Foundation for Medical Research, Chicago, 1930-1937, vol. 1, no. 10. (*b*) Pratt, J. H.: Dilution and Concentration Tests of Renal Function, Boston M. & S. J. **195**:203-207 (July 29) 1926. (*c*) Ellis, L. B., and Weiss, S.: Normal Variations in Renal Function with a Discussion of Their Physiological Significance, Am. J. M. Sc. **186**:233-242, 1933; (*d*) Renal Function in Persons with One Kidney, ibid. **186**: 242-248, 1933; (*e*) Renal Function in Arterial Hypertension, J. A. M. A. **100**: 875-878 (March 25) 1933. (*f*) Chapman, E. M., and Halstead, J. A.: Fractional Phenolsulphonphthalein Test in Bright's Disease, Am. J. M. Sc. **186**:223-232, 1933. (*g*) Van Slyke, D. D.; Stillman, E.; Modler, E.; Ehrich, W.; McIntosh, J. F.; Leiter, L.; Mackon, E. M.; Hannon, R. R., and Moore, N. S.: Observation on the Course of Different Types of Bright's Disease and on the Resultant Change in Renal Anatomy, Medicine **9**:257-386, 1930. (*h*) Kisch, F.: Essential Hypertension and the Kidneys, Wien. Arch. f. inn. Med. **9**:1, 1925; abstracted, J. A. M. A. **84**:239 (Jan. 17) 1925. (*i*) Major, R. H.: Renal Function in Arterial Hypertension, Am. J. M. Sc. **176**:637-644, 1928. (*j*) Musser, J. H., and Phillips, A. W.: A Comparison of Blood Pressure, Blood Urea Nitrogen, Phenolsulphonephthalein and Urine Tests in the Aged, J. Lab. & Clin. Med. **15**:632-637, 1930. (*k*) Buck, R. W., and Proger, S. H.: Dilution and Concentration Test of Renal Function, New England J. Med. **203**:1283-1288 (Dec. 25) 1930. (*l*) Freyberg, R. H.: The Choice and Interpretation of Tests of Renal Efficiency, J. A. M. A. **105**:1575-1580 (Nov. 16) 1935.

bilities of the tests. We have tried other methods of analysis in order to exhaust the possibilities of these tests.

The purpose of this paper is to demonstrate that in spite of apparently small differences from normal there exists a significant reduction in the ability of the kidneys of patients with essential hypertension to concentrate urine and to excrete phenolsulfonphthalein. This reduction can be demonstrated only when the study includes data on hypertensive patients and on normal persons considered collectively for the respective groups instead of singly in individual comparisons. In addition, it will be shown that the age of the patient and the duration of the disease have no effect on the renal function either of normal or of hypertensive persons. It will be shown that increase in the severity of the disease, as indicated by a rise in diastolic pressure, is accompanied by reduction in renal function. It will also be demonstrated that the use of alkaline diets apparently causes delay in excretion of fluids.

METHOD

As reported before the Sixth Pacific Science Congress,[2] we have performed tests of renal function on a group of 100 patients with essential hypertension and have compared the results with those obtained from tests on a group of normal subjects. In this study case histories of hospitalized patients were selected, each of whom had been subjected to at least six of eight different tests of renal function. At the time of the tests precautions were taken to eliminate extrarenal factors that might affect the outcome. Previous intake of nutrients was controlled,[1b] and dehydration through exercise and nervousness was prevented. Patients with anasarca were excluded. Extreme care was exercised in the collection of samples of urine, and drugs, such as sodium bicarbonate, were not given in a test period. Phenolsulfonphthalein excretion, urea clearance and the ability of the kidneys to concentrate the urine were measured in the following manner:

1. Phenolsulfonphthalein,[3] accurately measured in a tuberculin syringe, was given intravenously after emptying of the bladder and ingestion of 600 cc. of water. The result was reported in terms of the amount excreted at the end of two hours.

2. The recommended technic for measuring urea clearance was strictly adhered to.[4] Four hundred cubic centimeters of water was ingested at the beginning of the test in the hope of securing a maximum secretion, but frequently the rate

2. Dalton, J. W., and Nuzum, F. R.: Some Evidence of Impaired Function of the Kidney in Individuals with Essential Hypertension, Proc. Sixth Pacific Sc. Cong., to be published.

3. Rountree, L. G., and Geraghty, J. T.: An Experimental and Clinical Study of the Functional Activity of the Kidneys by Means of Phenolsulphonephthalein, J. Pharmacol. & Exper. Therap. **1**:579-661, 1910.

4. Møller, E.; McIntosh, J. F., and Van Slyke, D. D.: Studies in Urea Excretion: II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, J. Clin. Investigation **6**:427-465, 1928.

of formation of urine fell below 2 cc. per minute. The values obtained for the first and the second hour were averaged. The result was expressed in terms of the percentage of normal.

3. The concentration test of Volhard[5] was begun at 7 a. m. after the bladder had been emptied. The subject consumed quickly 1,000 cc. of water flavored with orange juice. Thereafter, a dry diet was given. Specimens of urine were collected at two hour intervals until 7 p. m. A single specimen was collected between 7 p. m. and 7 a. m. The volume of urine was measured within 5 cc. by standardized hydrometers, with correction for changes in temperature when indicated.

The six hour output, the total day output and the total night output of urine, originally divisions of the Volhardt test, are listed under separate headings for the sake of clarity and ease of study. In consideration of the effect of diet other tests include the twenty-four hour output of urine and the p_H of the urine.

After applying formulas applicable to groups of random samples, the statistical analysis was made by the computation of the means of the standard deviations through the use of the respective formulas of Fisher[6] and Burn.[7] Because of the large volume of calculation and the limitation of space, the positive results are summarized in suitable tables. All negative results have been previously reported in detail.[2]

OBSERVATIONS

Before comparing the results of renal function tests on a group of hypertensive patients with the results of the same tests on normal subjects, four variable conditions should be considered. The first of these variable conditions is the effect of the age of the subject on the function of the kidney. This variable is discharged in the following arrangement.[8] The samples are grouped according to decades in order to determine the significance of age in the variations of the readings.

	Number of Subjects	
Age, Yr.	Hypertensive	Normal
20 - 30	6	7
31 - 40	7	9
41 - 50	19	6
51 - 60	24	10
61 - 70	35	6
71 - 80	9	6
	100	44

A comparison is made, first, between the results of the renal function tests on patients with hypertension and the results of the same tests

5. Volhard, F., and Suter, F.: Nieren und ableitende Harnwege, Berlin, Julius Springer, 1931, p. 165.

6. Fisher, R. A.: Statistical Methods for Research Workers, London, Oliver & Boyd, 1930, p. 46.

7. Burn, J. H.: Errors in Biological Assay, Physiol. Rev. **10**:165, 1930.

8. Fisher,[6] p. 107.

on normal subjects of the same decades. In continuing the test of the effect of age on renal function, another method is used. Comparison of the means of the results of tests on patients with hypertension of two consecutive decades is made, as well as a like comparison for the normal subjects of the same two periods. This is accomplished by a simple rearrangement of the data so that the 6 hypertensive patients of the decade 20-30 are compared with the hypertensive subjects of the decade 31-40, and so on. In like manner, the 7 normal subjects of the decade 20-30 are compared with the 9 normal subjects of the decade 31-40. In these studies of the effect of age on the function of the kidney the chances of an insignificant difference in both series occurred as often as one time in sixty, or even more frequently.[2] It is felt that such an occurrence is too frequent and that apparent differences due to age are fortuitous.

The second of the four important variables affecting the study of renal function in essential hypertension is the relation of the duration of the process to the degree of impairment of renal function. The data on the patients with hypertension are arranged by test into six groups, one for each of the following tests: total day output of urine, total night output of urine, six hour output of urine, specific gravity difference, phenolsulfonphthalein excretion and urea clearance. Each of the six groups is divided according to the known duration of the disease into the following eight divisions: durations of one, two, three, four, five, six to nine, ten to fourteen and fifteen to eighteen years, respectively. The results of the determinations of all other divisions are compared separately with those of the first division, one year's duration. These collations have been published.[2] The one computation in this study which proved existence of actual differences was the phenolsulfonphthalein excretion for the division six to nine years' duration when compared with that for the division one year's duration. It must be remembered that there are forty-one other computations in this group of determinations testing this variable. Thus, one positive result in forty-two calculations is not outstanding, and one is forced to conclude that the duration of essential hypertension has no effect on the degree of impairment of function.

The third important variable to study is the coexistence of varying degrees of hypertension and changes in renal function, as shown by the same tests. The data on all hypertensive patients are arranged in six groups, one for each test used. Each of these groups has three divisions. Data on patients whose blood pressures were recorded as under 200 systolic and 99 diastolic are used as a basis of comparison. To this standard, in the first division, are compared data for the group having the same systolic pressures but having diastolic pressures ranging from 100 to 140. In the second and the third division to the data for the standard group are compared results for groups in which the systolic pressures are over 200 and the diastolic pressures are, respectively,

100 to 140 and 140 to 176. In table 1 is the summation of the results of these comparisons of the effects of extremes of hypertension on renal function.

In the third division in the phenolsulfonphthalein test the value for *P* (probability of insignificant difference) is less than 0.01. In the specific gravity test for the same division this value is just greater than

TABLE 1.—*Effect of Degree of Hypertension on Renal Function* *

Test		Degree of Hypertension: Systolic 150 - 200, Diastolic 100 - 140	Systolic 200 or More, Diastolic 100 - 139	Systolic 200 or More, Diastolic 140 - 176
Total day output of urine	x	1,034.1 cc.	1,034.1 cc.	1,084.1 cc.
	y	962.1 cc.	932.5 cc.	919.5 cc.
	x—y	72.0 cc.	101.6 cc.	114.6 cc.
	n	63	45	37
	P	0.4	0.4	0.4
Total night ouput of urine	x	315.7 cc.	315.7 cc.	315.7 cc.
	y	367.2 cc.	355.8 cc.	522.9 cc.
	x—y	51.5 cc.	40.1 cc.	207.2 cc.
	n	63	45	36
	P	0.4	0.4	0.02
Six hour output of urine	x	794.4 cc.	794.4 cc.	794.4 cc.
	y	675.1 cc.	675.1 cc.	517.6 cc.
	x—y	119.3 cc.	119.3 cc.	276.8 cc.
	n	61	45	37
	P	0.1	0.1	0.02
Specific gravity difference	x	1.0171 Gm./cc.	1.0171 Gm./cc.	1.0171 Gm./cc.
	y	1.0179 Gm./cc.	1.0162 Gm./cc.	1.0116 Gm /cc.
	x—y	—0.0008 Gm./cc.	0.0009 Gm./cc.	0.0055 Gm./cc.
	n	61	45	37
	P	0.7	0.5	0.01 †
Phenolsulfonphthalein excretion	x	59.0%	59.0%	59.0%
	y	59.2%	54.2%	37.5%
	x—y	—0.2%	4.9%	21.5%
	n	62	45	37
	P	0.9	0.2	0.01 †
Urea clearance, per cent of normal	x	65.8	65.8	65.8
	y	68.2	60.0	64.4
	x—y	—2.4	5.8	1.4
	n	63	45	37
	P	0.7	0.7	0.9

* The following symbols have been employed: P, the probability of insignificant difference; n, the number of samples (both of x and y); x, the means of the results of tests on hypertensive patients with systolic pressures of 150 to 200 and diastolic pressures from normal to 99, and y, the means of the results of tests on hypertensive patients with systolic and diastolic pressures as indicated in the three columns under the heading Degree of Hypertension.

† Any difference in means that is significant is indicated by a value for P of 0.01 or less.

0.01. Therefore, the chances of an insignificant difference occurring are less than one in one hundred and between one in fifty and one in one hundred, respectively. The chances of an insignificant difference are nearly one in fifty in the total night output test and the six hour output test in the same division, as indicated by values for *P* of 0.02. Four differences in the foregoing study are important. As the number of samples is large, it is only necessary to test these four computations

by a more accurate method.[9] The results of the new calculations are shown in table 2.

The values obtained from the two tests are comparable. The quantity for *P* is determined, which again indicates the chances for insignificant difference. There is complete substantiation of the results of the phenolsulfonphthalein excretion test in this new computation. The six hour output test, likewise, shows a real difference between the two means of the two extremes of hypertension. The total night output test and the specific gravity test allow an insignificant difference between the two means of one to five and one to twenty, respectively. In this more accurate study there are two instances out of eighteen computations in which unquestionable differences between means occur.

TABLE 2.—*Effect of Degree of Hypertension on Renal Function* *

Test		Degree of Hypertension: Systolic 150 to 200, Diastolic Normal to 99		Degree of Hypertension: Systolic 200 or Over, Diastolic 140 to 176
Total night output of urine	Mean	315.7 cc.		522.9 cc.
	Standard deviation of the mean	27.4		149.5
	Difference		207.2 cc.	
	P		0.18	
Six hour output of urine	Mean	794.4 cc.		517.6 cc.
	Standard deviation of the mean	74		68.1
	Difference		276.8 cc.	
	P		0.01 *	
Specific gravity difference	Mean	1.0171 Gm./cc.		1.0116 Gm./cc.
	Standard deviation of the mean	0.0009		0.0026
	Difference		0.0055 Gm./cc.	
	P		0.05	
Phenolsulfonphthalein excretion	Mean	59.0%		37.5%
	Standard deviation of the mean	2.90		6.6
	Difference		21.5%	
	P		0.01 *	

* Any difference in means is significant if indicated by a value for P of 0.01 or less.

The fourth variable which should be considered is the effect of the alkalinity of the diet on the function of the kidney in hypertension. All of the patients with hypertension mentioned so far are from a group studied since 1932. These patients were given a general diet, the ash of which was neutral. They were not given alkaline medication. Prior to 1932, as a result of studies on 1 of us,[10] all patients with essential hypertension were placed on basic or semibasic diets. The renal function of these patients on alkaline diets was studied through the use of the Volhard concentration and the phenolsulfonphthalein excretion

9. Fisher,[6] pp. 101-102. Burn,[7] p. 168.

10. Nuzum, F. R.; Sansum, W. D., and Osborne, M.: The Experimental Production of Hypertension, Arch. Int. Med. **35**:497-499 (April) 1925.

test only. The sole test of the effect of the diet as an alkalinizing agent was the determination of the p_H of the urine. If more than one reading of the p_H was taken, an average was made. All patients were on the alkaline diet for one month before observations were started. The results of the tests from 36 records, from 1928 to 1932, are analyzed statistically and compared with the records of the same tests on a group of 71 patients, selected at random from the 100 patients with hypertension who were on the general diet. Because of the limited series of patients on the alkaline diet no subjects in the early adult years are included. This should make little difference, for it has been shown that age does not affect the function of the kidney as illustrated by the six tests of renal function considered. The data are derived from the results of the tests on patients in the following decades:

	No. of Subjects	
Decade	General Diet	Alkaline Diet
41 - 50	10	5
51 - 60	24	12
61 - 70	28	14
71 - 80	9	5
	71	36

The appropriate formula [11] is applied to the means and the standard deviation of the means of the two larger groups in order to determine the standard error. The results are summarized in table 3.

Between respective tests, the p_H, the total day output, the total night output and the six hour output test, of the diet groups significant differences occur more frequently than ninety-nine times in one hundred. To determine any effect on water balance due to retention of fluid because of diet, the total twenty-four hour output of urine is determined by the summation of the total day and the total night output. As is seen in table 3, there is no consequential difference in the means of the determinations of the twenty-four hour output.

Since it has been shown that the age of the patient and the duration of the disease have no effect on renal function as illustrated by the six tests considered, the results of the study of the patients with hypertension and the observations on normal subjects are divided into six groups each, according to the tests used. Thus the means and their standard deviation are computed, all ages and durations included with the use of the formulas for standard error.[11] The summary of this collation is recorded in table 4.

11. Fisher,[6] pp. 101-102.

TABLE 3.—*Comparison of the Effect of a General Diet and the Effect of an Alkaline Diet on the Renal Function of Patients with Hypertension*

Test		Diet: General Diet		Diet: Alkaline Diet
p_H of urine	Mean	6.4		7.25
	Standard deviation of the mean	0.08		0.06
	Difference		0.85	
	P		0.01 *	
Total day output of urine	Mean	953.0 cc.		724.0 cc.
	Standard deviation of the mean	43.1		45.2
	Difference		229.0 cc.	
	P		0.01 *	
Total night output of urine	Mean	372.0 cc.		574.0 cc.
	Standard deviation of the mean	29.0		50.5
	Difference		202.0 cc.	
	P		0.01 *	
Six hour output of urine	Mean	638.0 cc.		497.0 cc.
	Standard deviation of the mean	33.6		47.0
	Difference		191.0 cc.	
	P		0.01 *	
Total twenty-four hour output of urine	Mean	1,819.2 cc.		1,299.2 cc.
	Standard deviation of the mean	48.6		55.1
	Difference		20.0 cc.	
	P		0.8	
Specific gravity difference	Mean	1.0149 Gm./cc.		1.0140 Gm./cc.
	Standard deviation of the mean	0.0007		0.0011
	Difference		0.0009 Gm./cc.	
	P		0.615	
Phenolsulfonphthalein excretion	Mean	53.0%		59.0%
	Standard deviation of the mean	2.0		2.7
	Difference		6.0%	
	P		0.09	

* Any difference in means that is significant is indicated by a value for P of 0.01 or less.

TABLE 4.—*Renal Function in Grouped Patients with Essential Hypertension and Grouped Normal Subjects as Illustrated by the Results of Common Clinical Tests*

Test		Blood Pressure: Hypertensive		Blood Pressure: Normal
Total day output of urine	Mean	943.0 cc.		1,013.0 cc.
	Standard deviation of the mean	35.3		48.2
	Difference		70.0 cc.	
	P		0.24	
Total night output of urine	Mean	377.5 cc.		309.0 cc.
	Standard deviation of the mean	26.7		27.1
	Difference		68.5 cc.	
	P		0.07	
Six hour output of urine	Mean	700.0 cc.		772.0 cc.
	Standard deviation of the mean	30.2		41.0
	Difference		71.0 cc.	
	P		0.15	
Specific gravity difference	Mean	1.0163 Gm./cc.		1.0204 Gm./cc.
	Standard deviation of the mean	0.0006		0.0011
	Difference		0.0041 Gm./cc.	
	P		0.01 *	
Phenolsulfonphthalein excretion	Mean	55.5%		63.2%
	Standard deviation of the mean	1.085		2.28
	Difference		7.7%	
	P		0.01 *	
Urea clearance, percentage of normal urine	Mean	65.5		63.5
	Standard deviation of the mean	2.56		3.05
	Difference		2.2	
	P		0.58	

* Any difference between means that is significant is indicated by values for P of 0.01 or less.

With the value for P less than 0.01 the differences between the hypertensive patients and the normal subjects in the fixation of specific gravity and the excretion of phenolsulfonphthalein are highly significant. Thus two of six determinations in this study offer a real difference between the renal function of a group of patients with essential hypertension and the renal operation of a group of normal subjects.

COMMENT

Although an adjunct rather than a mainstay of proof, statistical analysis is necessary in order more clearly to define the values at issue. Certain criticism of methods is valid. It is true that the numbers of samples in certain groups are small. Even so, an indication of a trend can be traced. It may be said that there is a violation in theory, at least, of the prerequisites of the random sample. Three major limitations to such sampling are unavoidable. All of these patients were hospitalized; all had dietary and therapeutic restrictions, and all had to have six tests performed during one hospitalization.

These statistical analyses and the subsequent results are made more easily understandable when it is emphasized that these results are from the study of a group of hypertensive patients and a group of normal subjects as groups and not from a comparison of the individuals forming each group. From a practical point of view the differences demonstrated here might not be elicited between any 2 individuals selected at random as representative of their respective groups. As such, these tests are not practical as clinical laboratory methods for demonstration of impairment of renal function in an isolated patient suspected of having essential hypertension, as may only be illustrated by computations derived from large numbers of hypertensive patients and normal subjects taken as groups.

From the study of the first and the second variable, there is little doubt that within the limits of these tests there is evidence that the age of a subject and the duration of hypertension have no effect on concentration or excretion by the kidney, either in patients with hypertension or in normal persons.

With an increase of diastolic pressures to extremes there coexists a caducous excretion of phenolsulfonphthalein. A decrease in the six hour output of urine may possibly be present, indicating an increase in renal impairment in patients with excessive diastolic pressures, although such changes in function may be due to a delay in excretion of urine.

At the time when alkaline diet was used extensively in the treatment of patients with essential hypertension the only check on the effects of this diet was the p_H of the urine. Although the only change in the management of some of our patients was the substitution of an alkaline

diet, it is a just criticism [12] that the variation in the excretion of the urine noted in the studies on alkaline diet cannot be proved to be due to the alkalinity of a patient as controlled by the diet. However, at the time the alkaline diet was used, the patients had a definite variation in renal excretion from those patients on the general diet. The fixation of the specific gravity was the same in both groups. Although there is no apparent retention of fluid in the tissues of hypertensive patients using the alkaline diet, as indicated by the equivalent volumes in the twenty-four hour output of urine of the two groups, there is a definite delay in excretion of urine, as is seen in the reduction of the six hour output and the total day output, with the compensatory increase in the night output.

In collecting the results of tests on patients in all decades according to the tests performed in the study summarized in table 4, one can note definite differences between two of the renal function tests in groups of patients with essential hypertension and groups of normal subjects. There is evidence of fixation of the specific gravity of the urine which with the reduction in ability to excrete phenolsulfonphthalein, is evidence of impairment of the function of the kidney in patients with essential hypertension. In the presence of the fixation of the specific gravity there is no increase in the volume output of the urine, which is the usual compensatory action in other types of renal disease with specific gravity fixation.[13] Although definite, the difference between the means in the specific gravity tests is not great. This in itself is a possible explanation of the lack of variation from normal of the rate and the time of urine output. The reduction in excretion of phenolsulfonphthalein must be due to delay in glomerular filtration. There is no variation in fluid loss due to insensible perspiration in the absence of sweat in circulatory disease.[14]

SUMMARY

Instead of studying differences between single examples and noting variations between two random single samples, a more sensitive observation is made by comparing the results of renal function tests on patients with essential hypertension as a group with results of the same tests on normal subjects as a group.

Working even in this manner we find that there is no variation of the renal function from the normal in a patient with essential hypertension because of the age of the patient or because of the duration of the disease.

12. Lucia, S. P.: Personal communication to the authors.

13. Lashmet, F. H., and Newburgh, J. H.: A Comparative Study of the Excretion of Water and Solids by Normal and Abnormal Kidneys, J. Clin. Investigation **11**:1003-1010, 1932.

14. Dubois, E. F.: Basal Metabolism in Health and Disease, ed. 3, Philadelphia, Lea & Febiger, 1936, p. 446.

There is a retardation of the flow of urine in patients with hypertension having high diastolic pressures.

There is some indication of retardation of urinary flow and compensatory nocturia in hypertensive patients on an alkaline diet.

In general, there is fixation of specific gravity and retardation of phenolsulfonphthalein output in patients with hypertension.

The Volhard concentration and the phenolsulfonphthalein excretion test themselves are of no use clinically for the differential diagnostic purpose of distinguishing between persons with essential hypertension and normal persons in isolated instances. These studies indicate variation in the physiologic processes of the kidney due to a disease process coexistent with essential hypertension.

Dr. A. J. Lotka and Dr. N. R. Blatherwick of the Metropolitan Life Insurance Company assisted us and criticized our statistical methods. They expressed the belief that the conclusions drawn are essentially justifiable. All calculations have been checked and conclusions verified by H. H. Ritchie, Chairman, Department of Mathematics, Santa Barbara Junior High School. Dr. Fritz Bischoff, Chairman, Department of Research, Santa Barbara Cottage Hospital, offered criticism and assisted us in our analysis.

All computations are on file in the Department of Research, Santa Barbara Cottage Hospital. They are available for the use of other investigators for comparison or as an adjunct to their work.

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EFFECT OF ULCER ON ACIDITY AND NEUTRALIZING ABILITY IN DUODENAL BULB

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The preponderance of the investigation dealing with the pathogenesis and the maintenance of chronic duodenal ulcer has been concerned with the acid gastric juice. A large amount of work has been reported tending to incriminate this factor and designed to determine the best means of combating and alleviating its ill effects. As a consequence, clinical attention has been narrowly focused on the acidity in the stomach, while the acidity in the duodenum has been almost entirely neglected. In order to evaluate adequately the role of the acid gastric juice in duodenal ulcer, it is essential to know what effect the acid chyme has on the reaction and the neutralizing ability at the actual site of the ulcer—the duodenal bulb.

The contents of the first part of the duodenum in normal persons have been shown to possess an ability to neutralize, buffer and dilute gastric chyme which is generally very efficient.[1] In contradistinction to normal subjects, however, most patients with duodenal ulcer exhibit gastric hyperacidity and hypersecretion.[2] It is problematic whether a

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1. Berk, J. E.; Rehfuss, M. E., and Thomas, J. E.: The Acidity of the "Ulcer-Bearing Area" of the Duodenum in Normal Persons, Am. J. Digest. Dis. **9**:276, 1942.

2. (*a*) Alvarez, W. C.: Standards of Normal in Gastric Secretion, Ann. Int. Med. **6**:315, 1932. (*b*) Bloomfield, A. L.: Clinical Aspects of Gastric Secretion, ibid. **6**:307, 1932; (*c*) The Problem of Gastric Hyperacidity, Am. J. Digest. Dis. **6**:700, 1939. (*d*) Bloomfield, A. L., and Polland, W. S.: The Diagnostic Value of Studies of Gastric Secretion, J. A. M. A. **92**:1508 (May 4) 1929. (*e*) Bloomfield, A. L.; Chen, C. K., and French, L. R.: Basal Gastric Secretion as a

(Footnote continued on next page)

patient with ulcer with a scarred, contracted, irritable duodenal cap into which there is being emptied excessive amounts of acid gastric juice displays a similar neutralizing efficiency. On the answer to this question rests in part some insight into the physiologic defects in ulcer; only through its answer can the acid factor in duodenal ulcer be properly evaluated.

Several investigators have endeavored to determine the duodenal reaction in patients with duodenal ulcer,[3] but Morton alone [4] concerned himself with the important "ulcer-bearing" duodenal cap. Patients with peptic ulcer, he found, displayed higher values and wider variations in duodenal bulb acidity than did normal persons. The most constant feature in the patients with ulcer was the more or less uniform presence of titratable free acid in the contents of the first part of the duodenum.

Clinical Test of Gastric Function with Special Reference to Peptic Ulcer, J. Clin. Investigation **19**:863, 1940. (*f*) Bockus, H. L.; Glassmire, C., and Bank, J.: Fractional Gastric Analysis in Two Hundred Cases of Duodenal Ulcer, Am. J. Surg. **12**:6, 1931. (*g*) Cheney, G., and Bloomfield, A. L.: Gastric Function in Cases of Gastric and Duodenal Ulcer, J. Clin. Investigation **5**:511, 1928. (*h*) Comfort, M. W., and Osterberg, A. E.: Gastric Secretion After Stimulation with Histamine in the Presence of Various Types of Gastric and Duodenal Lesions, J. A. M. A. **97**:1141 (Oct. 17) 1931. (*i*) Hurst, A. F.: Hyperesthenic Gastric Diathesis, Lancet **2**:1369, 1922. (*j*) Hurst, A. F., and Venables, J. F.: The True Incidence of Hyperchlorhydria in Gastric and Duodenal Ulcer, Guy's Hosp. Rep. **79**:249, 1929. (*k*) Polland, W. S.: Histamine Test Meals: An Analysis of Nine Hundred and Eighty-Eight Consecutive Tests, Arch. Int. Med. **51**:903 (June) 1933. (*l*) Rehfuss, M. E.: Possibilities of Fractional Gastric Analysis, J. A. M. A. **71**:1534 (Nov. 9) 1918; (*m*) The Diagnosis and Treatment of Diseases of the Stomach, Philadelphia, W. B. Saunders Company, 1927. (*n*) Ruffin, J. M., and Dick, M.: The Significance of Gastric Acidity After Histamine Stimulation: A Statistical Study of 2,877 Gastric Analyses, Ann. Int. Med. **12**: 1940, 1939. (*o*) Vanzant, F. R.; Osterberg, A. E.; Alvarez, W. C., and Rivers, A. B.: Studies of Gastric Pepsin: II. Secretion of Pepsin in Cases of Duodenal Ulcer and Pseudo-Ulcer, J. Clin Investigation **12**:557, 1933. (*p*) Vanzant, F. R.; Alvarez, W. C.; Berkson, J., and Eusterman, G. B.: Changes in Gastric Acidity in Peptic Ulcer, Cholecystitis and Other Diseases Analyzed with the Help of a New and Accurate Technic, Arch. Int. Med. **52**:616 (Oct.) 1933.

3. (*a*) Einhorn, M.: Experiences with the Duodenal Contents, J. A. M. A. **55**:6 (July 2) 1910; (*b*) Fractional Examination of the Duodenal Contents in Peptic Ulcer, ibid. **72**:1471 (Nov. 5) 1921; (*c*) The Duodenal Tube and Its Possibilities, Philadelphia, F. A. Davis Company, 1926. (*d*) Einhorn, M., and Rosenbloom, J.: A Study of the Duodenal Contents in Man, Arch. Int. Med. **6**:666 (Dec.) 1910. (*e*) Kearney, R. W.; Comfort, M. W., and Osterberg, A. E.: Hydrogen Ion Concentration of the Duodenal Contents Under Fasting Conditions in Normal Persons and in Patients with Duodenal Ulcer: A Comparative Study, J. Clin. Investigation **20**:221, 1941. (*f*) Morton, C. B.: Observations on Peptic Ulcer: VI. Preliminary Report of Clinical Experiments with Gastro-Duodenal Analysis, Am. J. M. Sc. **177**:65, 1929; (*g*) Observations on Peptic Ulcer, South. Surgeon **3**:316, 1934.

4. Morton, footnotes 3*f* and *g*.

Morton's work, however, has several shortcomings; there was uncertainty as to the precise position of the tip of the duodenal tube throughout the period of observation, for the most part only single samples were removed and p_H determinations were not made.

The present communication represents the results of an inquiry into the acidity and the neutralizing ability of the duodenal bulb contents in patients with duodenal ulcer through the use of a method which largely meets the objections raised to previous investigations.[5] It was hoped that the information gained would contribute to a solution of some of the problems which have been posed and would provide better criteria with which to judge the role of the acid gastric juice in duodenal ulcer.

MATERIAL

From the wards and from the outpatient gastrointestinal disease clinic of the Jefferson Hospital 19 patients were chosen at random, all of whom at the time were complaining of symptoms referable to an ulcer and all of whom gave radiologic evidence of an active, nonobstructive duodenal ulcer without any demonstrable lesion in the stomach. A number had had previous episodes of bleeding, and in the few who had been subjected to gastroscopic examination no evidence of gastritis or gastric ulcer was found.

Of the entire group studied 17 persons (12 men, 5 women) were selected for the purpose of this presentation because the experiments performed on them were considered satisfactory from the technical viewpoint. The 17 ranged in age from 21 to 59 years, with an average age of 42.7 years. The men ranged from 21 to 57 years of age, with an average of 42.5 years, and the women from 21 to 59 years of age, with an average of 43.2 years.

METHOD

Each patient was studied in the morning before breakfast and after a twelve hour fast. Through the use of a specially constructed double lumen tube and a method which permitted more or less constant fluoroscopic control as well as roentgenographic proof of the position of the tube,[5] specimens were simultaneously withdrawn at ten minute intervals from the pyloric antrum and from the duodenal cap. Samples were collected for one-half hour in the fasting state and for two hours after the feeding of an Ewald meal consisting of two pieces of stale bread or dry toast and 250 cc. of tap water.

On each gastric and duodenal sample the p_H was determined at once through the use of a Leeds-Northrup p_H indicator, which employs a glass electrode. The free and the total acidity of each specimen was titrimetrically estimated after filtration, Toepfer's reagent and phenolphthalein being used as the respective color indicators.[6] On each duodenal sample, in addition, there was determined what was called the excess neutralizing ability. This consisted of the amount of

5. Berk, J. E.; Rehfuss, M. E., and Thomas, J. E.: A Method for the Simultaneous Aspiration of the Contents of the Stomach and First Part of the Duodenum, J. A. M. A. **119**:259 (May 16) 1942.

6. Berk, J. E.; Thomas, J. E., and Rehfuss, M. E.: Limitations in the Use of Color Indicators in Gastric Analysis, Am. J. Digest. Dis. **9**:106, 1942.

tenth-normal hydrochloric acid which it was necessary to add before Toepfer's reagent indicated a positive reaction for free acid.[7]

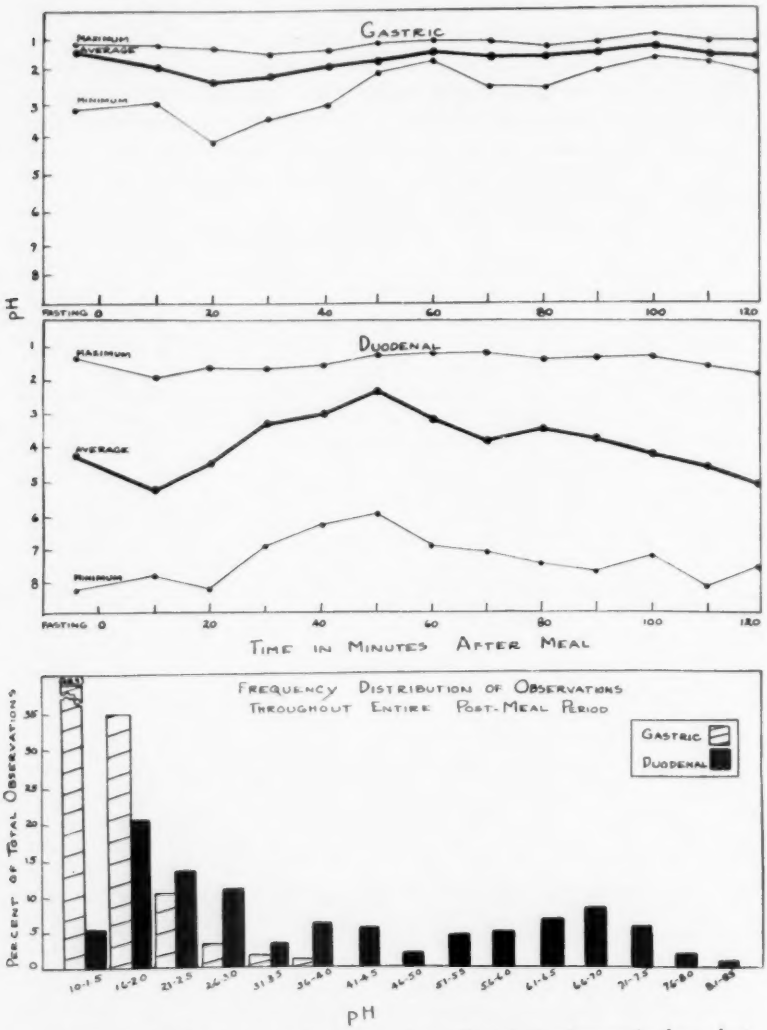

Chart 1.—Acidity in p_H units of samples collected simultaneously from just above and just below the pylorus.

7. Berk, J. E.; Thomas, J. E., and Rehfuss, M. E.: The Reaction and Neutralizing Ability of the Contents of the Pyloric Antrum and First Part of the Duodenum in Normal Dogs Following an Ewald Meal, Am. J. Physiol. **136**:157, 1942; footnote 5.

Of the 32 experiments which were made 23 were accepted as satisfactory from the standpoint of technic. These involved 2,202 separate determinations consisting of 633 determinations of p_H, 625 estimations of free acid, 625 estimations of total acidity and 319 determinations of excess neutralizing ability of the duodenal contents. The values for the four specimens obtained from each person in the fasting state were averaged and expressed as a single value.

RESULTS

Acidity in p_H Units (chart 1).—Stomach: As was to be expected, the hydrogen ion concentration of the stomach contents in patients with duodenal ulcer was much greater than that encountered in normal persons (an average postmeal p_H of 1.68, as compared with 2.78).[4] Not only was the average p_H lower, but the distribution range of the values was much narrower. Only 2 (0.88 per cent) of the 227 postmeal samples exhibited a p_H in excess of 3.5, the value which we had adopted as the critical one for free acid.[6]

Duodenum: The average postmeal duodenal p_H was also lower than that observed in normal persons (3.87, as compared with 4.94).[4] Although numerically the differences from the normal p_H in the stomach and in the duodenum of patients with ulcer were approximately equal, on a percentage basis the gastric p_H was 39.4 per cent, while the duodenal p_H was only 21.6 per cent, lower than the normal value. This fact strongly suggests that the reaction in the duodenal cap is only in part determined by the hydrogen ion concentration of the stomach contents and that increases in gastric acidity are not necessarily associated with equal increases in duodenal acidity.

Samples collected simultaneously from just above and just below the pylorus in patients with ulcer exhibited a consistent difference in p_H, just as did samples from normal persons. Surprisingly enough, the difference in the average postmeal value was as great (2.19 p_H units) as that displayed by normal persons (2.17 p_H units). In contradistinction to normal persons, in patients with ulcer the average postmeal p_H of the duodenal bulb contents not only fell below 3.5 but remained below this critical level for four consecutive readings (thirty to sixty minutes postcibal, inclusive). Furthermore, 53.9 per cent of all the post-Ewald-meal samples had positive reactions for free acid (p_H 3.5 or below), an increase of 70 per cent over the samples from normal persons fed the same meal.

A pronounced fluctuation in the reaction of the contents of the duodenum, especially in the first part, has been noted both in dogs [8]

8. Mann, F. C., and Bollman, J. L.: A Symposium Concerned with the Duodenal Factors in the Neutralization of Acid Chyme, Am. J. Digest. Dis. & Nutrition **2**:284, 1935.

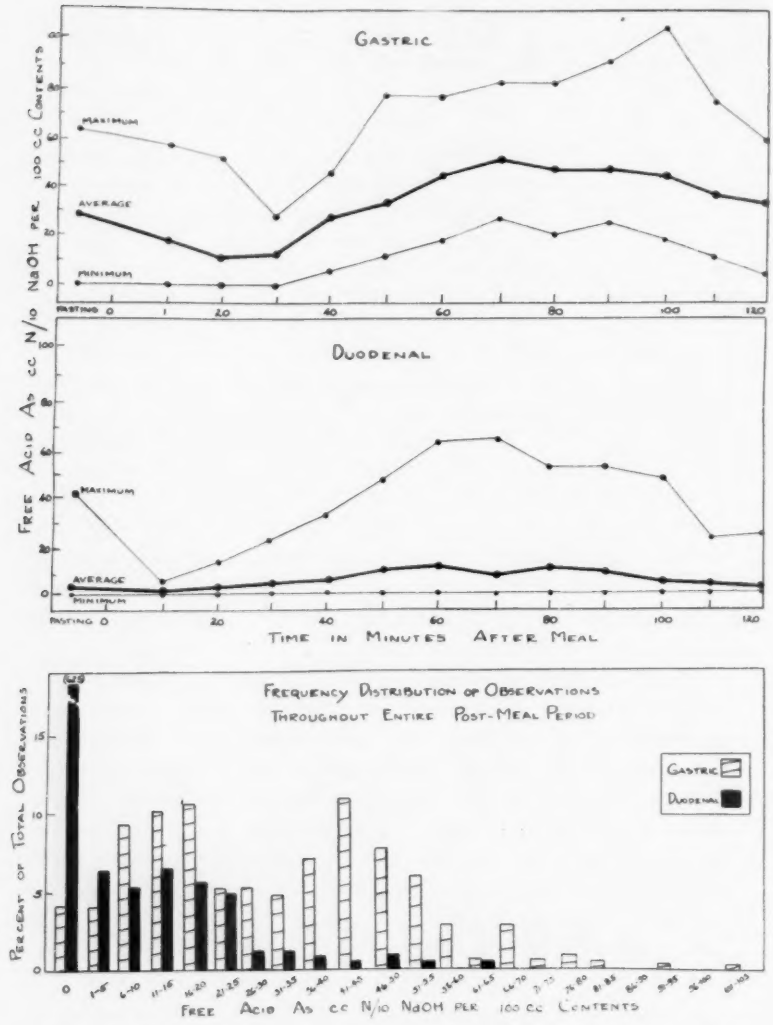

Chart 2.—Free acid as determined on samples collected simultaneously from just above and just below the pylorus.

and in man.[9] We did not observe this fluctuation in normal subjects, but a considerable degree of fluctuation in p_H readings was by no means uncommon in patients with duodenal ulcer. As a consequence, low p_H values were widely scattered throughout the various postmeal intervals, although most of the low readings tended to concentrate between the thirty and the seventy minute determinations.

The discrepancy in the configuration of the plotted values of the average p_H in the pyloric antrum and in the duodenal cap is worthy of special note. The relative independence of these curves shows that one cannot rely with any assurance on the gastric p_H as an index of the behavior of the p_H present over the same period of time in the first part of the duodenum.

Free Acid (chart 2).—Stomach: The distinct curve pattern of the plotted values for average gastric free acid was in sharp contrast to the relatively flat line assumed by the plotted values for average gastric p_H (chart 1). The pattern more closely simulated that of the average duodenal p_H (chart 1), yet a definite variation can be discerned.

Duodenum: Free acid as determined colorimetrically was found in the contents of the first part of the duodenum in 37.5 per cent of all the postmeal specimens. This frequency was much greater than that for normal persons.[1] In the colorimetric determinations of free acid our end point with Toepfer's reagent was just below p_H 3.5.[6] With our technic, however, the filtration and the dilution of the samples preparatory to titration introduce an error that results in some false negative readings.[6] We must assume, therefore, that all specimens with a p_H of 3.5 or less in the unfiltered and undiluted state contain free acid. On this basis over one half (53.9 per cent) of all the postmeal duodenal samples contained free acid; the corresponding value for normal subjects determined in the same way was slightly less than one third (31.7 per cent).

Colorimetrically 82.3 per cent and electrometrically 100 per cent of all the patients showed free acid in their duodenal bulb contents at some time during the postmeal phase. Colorimetrically 52.9 per cent and electrometrically 70.5 per cent of the patients showed free acid in three or more consecutive postmeal samples. These figures are much greater than similar ones determined for normal subjects.[1] Furthermore, free acid tended to persist for longer periods in the duodenum in patients with ulcer than in normal subjects; there was much less of a tendency toward rapid recuperation of neutralizing efficiency. This observation

9. Eyerly, J. B.: Comparative p_H Values Within the Stomach, Pylorus and Duodenum in Antacid Therapy, Am. J. Digest. Dis. **7**:431, 1940. Karr, W. G., and Abbott, W. O.: Intubation Studies of the Human Small Intestine: IV. Chemical Characteristics of the Intestinal Contents in the Fasting State and as Influenced by the Administration of Acids, of Alkalies and of Water, J. Clin. Investigation **14**:893, 1935. Kearney, Comfort and Osterberg.[3e]

is best illustrated by the fact that one half (52.9 per cent) of all the patients studied showed p_H values of 3.5 or less for six consecutive postmeal samples.

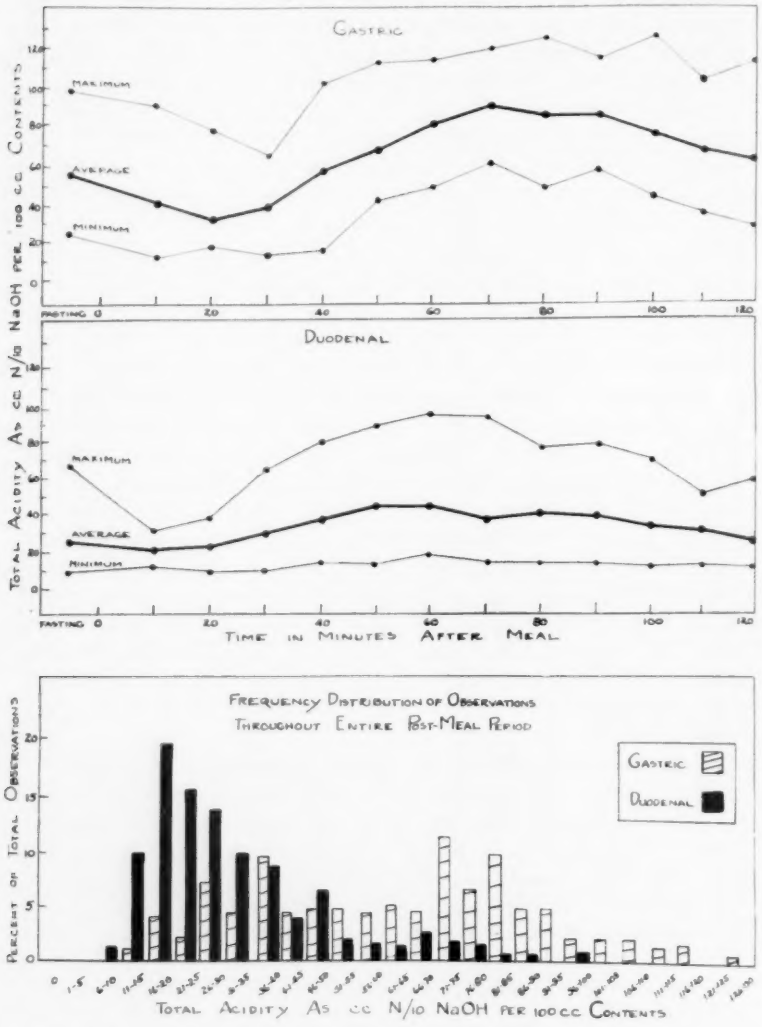

Chart 3.—Total acidity of samples collected simultaneously from just above and just below the pylorus.

Total Acidity (chart 3).—Stomach: The average gastric total acidity, like the free acid, was sharply different in curve pattern from

the average gastric p_H (chart 1). Even though the pattern bore a closer resemblance to the curve of the average duodenal p_H (chart 1), the parallelism was not close enough at all points to warrant reliance on gastric total acidity as a sure index of the behavior of the coexistent effective acidity in the duodenal bulb.

Duodenum: The lack of sharp agreement between the curve for average gastric and that for average duodenal total acidity should be

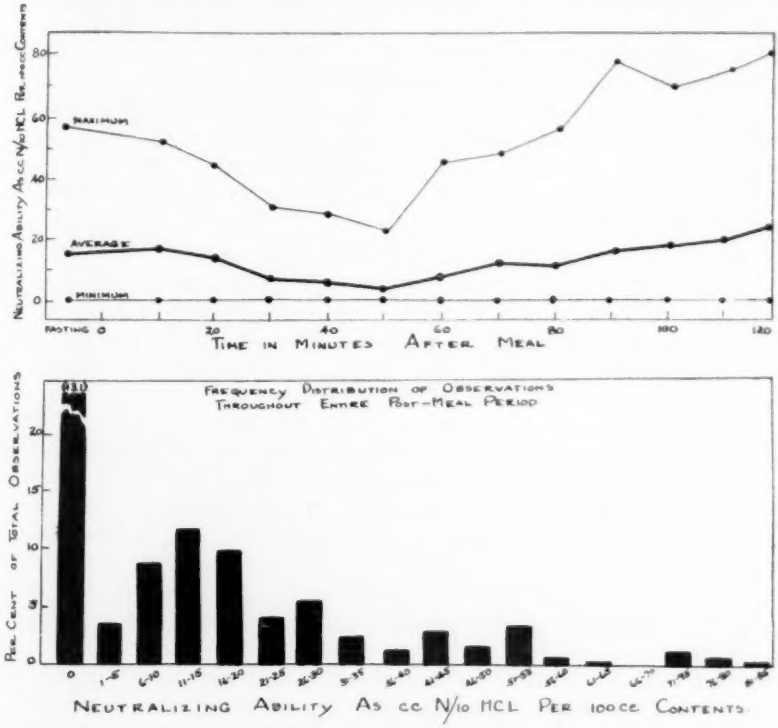

Chart 4.—Excess neutralizing ability of the contents of the first part of the duodenum.

noted. The slight but significant discrepancies between them is further indication of the absence of a constant relationship between the acidity simultaneously determined in the stomach and in the duodenal contents.

Excess Neutralizing Ability of the Duodenal Contents (chart 4).—Excess neutralizing ability has been defined[7] as a measure of the reserve capacity which the contents of the duodenal bulb possess to neutralize, buffer and dilute the chyme received from the stomach above that necessary to offset the free acid content.

More than two out of every five (43.1 per cent) of the postmeal duodenal samples failed to display any excess neutralizing ability as compared with less than one in every five (19.9 per cent) of the specimens obtained from normal subjects.[1] In added contrast to normal persons, however, patients with ulcer showed a much wider distribution range of values. It is a physiologic maxim that efficient regulatory mechanisms show narrow ranges. Wide departures from the average, therefore, as illustrated on the one hand by the greater number of specimens containing free acid or on the other by the higher range of values for excess neutralizing ability, are indicative of inefficiency of the duodenal neutralizing regulatory mechanism in patients with ulcer.

The rise in the value for average excess neutralizing ability during the second postprandial hour, when the values for gastric acidity were high, probably accounts for the concomitant increase in duodenal p_H and suggests that the duodenal neutralizing capacity was in the ascendancy during that period.

COMMENT

There are recognized deficiencies in the method of study employed which permit a fair amount of experimental error.[5] Our primary purpose in this presentation, however, was to compare patients with duodenal ulcer with normal persons in regard to the acidity and the neutralizing ability of the contents of the first part of the duodenum. The utilization, therefore, of the same method of study for the two groups affords an acceptable means of comparison, because any inherent experimental error is thereby equally applicable to each group.

The duodenal bulb is distinctly an acid area, especially in patients with duodenal ulcer. Its contents in such patients after an Ewald meal have an average p_H of about 3.9. This value indicates a hydrogen ion concentration in excess of that encountered in normal persons; still, it is above the critical level below which free acid is said to be present (p_H 3.5).

The ability of the contents of the first part of the duodenum to neutralize, buffer and dilute the gastric chyme is in evidence in patients with duodenal ulcer although impaired. Despite higher average values for gastric acidity, patients with duodenal ulcer are able to maintain an average difference in p_H between the contents of the pyloric antrum and the contents of the duodenal bulb which is as great as that in normal subjects. Nevertheless, as is best illustrated in the individual experiments, the neutralizing ability of the duodenal bulb in contrast to that of normal persons is overcome more frequently, to a greater extent and for longer periods of time. Electrometrically all the patients studied showed free acid (p_H 3.5 or less) in the duodenal bulb contents at some time during a two hour fractional period of observation after an Ewald meal; over one half of them displayed a positive reaction for free acid in six consecutive postmeal samples. The increased frequency

with which free acid is encountered in the contents of the first part of the duodenum, as well as the higher average acidity values, for patients with ulcer as compared with those for normal subjects confirms Morton's [4] findings.

The explanation for the increase in duodenal acidity in patients with duodenal ulcer would appear, offhand, to rest in the higher values for gastric acidity which they display. Earlier investigators, however, have called attention to an apparent lack of relationship between gastric acidity and duodenal acidity,[10] and we [1] have been able to demonstrate that in normal persons the duodenal reaction is affected to a lesser extent than would be expected from an increase in gastric hydrogen ion concentration. In the present study also there was some indication that increases in gastric acidity in patients with duodenal ulcer are not necessarily associated with increases in duodenal acidity of equal magnitude (chart 1). Hence, in regard to evaluation of the acid factor in duodenal ulcer, it becomes a matter of some importance whether or not the acidity at the site of the ulcer proper is determined only by the degree of acidity of the gastric chyme.

We undertook to answer this question in part by comparing the entire group of patients with duodenal ulcer available for study with 6 normal subjects specially selected because of their high values for gastric acidity (charts 5, 6, 7 and 8). The close parallelism between the acid titers in the two groups is easily apparent. It is noteworthy, however, that the normal subjects, particularly in the second half of the observation period, uniformly displayed higher gastric acid concentrations and at the same time lower duodenal acid concentrations than did the patients with duodenal ulcer. This, we hold, is evidence that the degree of acidity of the stomach contents is by no means the sole determinant of the degree of acidity of the duodenal bulb contents and that patients with duodenal ulcer differ from normal persons not only in the direction of gastric hyperacidity but in the direction of a defectiveness of the neutralizing capacity in the duodenal bulb. The sharp fluctuation in the reaction of the contents of the first part of the duodenum

10. The Fractional Examination of the Duodenal Contents, Am. J. M. Sc. **156**: 817, 1918. Friedenwald, J., and Sindler, J.: Fractional Analysis of the Duodenal Contents in Normal Individuals, J. A. M. A. **77**:1469 (Nov. 5) 1921. McClure, C. W., and Wetmore, A. S.: Studies in Pancreatic Function: Enzyme Concentration of Duodenal Contents After the Ingestion of Pure Foodstuffs and Food Mixtures by Normal Men, Boston M. & S. J. **187**:882, 1922. McClure, C. W.; Wetmore, A. S., and Reynolds, S.: Physical Characters and Enzymatic Activities of Duodenal Contents: Findings During Gastric Digestion in Normal Young Men, J. A. M. A. **77**:1468 (Nov. 5) 1921. Okoda, S., and Arai, M.: The Hydrogen Ion Concentration of the Intestinal Contents, J. Biol. Chem. **51**:135, 1922. Einhorn.[3b] Einhorn.[3c] Kearney, Comfort and Osterberg.[3e] Morton.[3f] Morton.[3g]

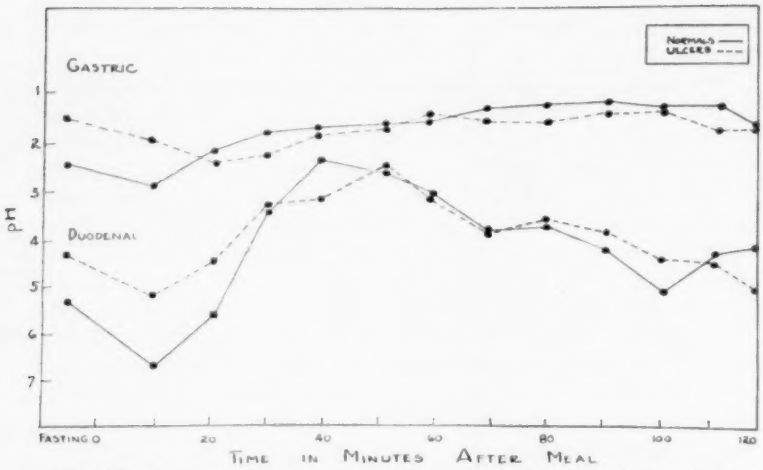

Chart 5.—Average acidity in p_H units of samples collected simultaneously from just above and just below the pylorus from patients with duodenal ulcer compared with that of samples from a group of normal subjects with gastric hyperacidity.

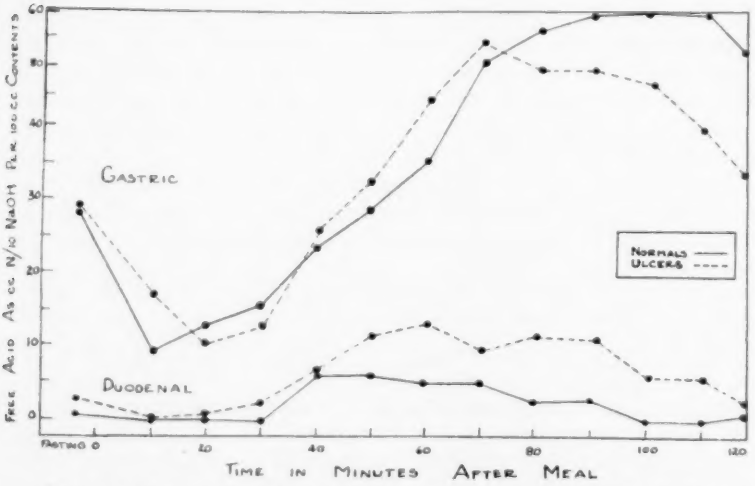

Chart 6.—Average free acid, as determined on samples collected simultaneously from just above and just below the pylorus of patients with duodenal ulcer compared with that of a group of normal subjects with gastric hyperacidity.

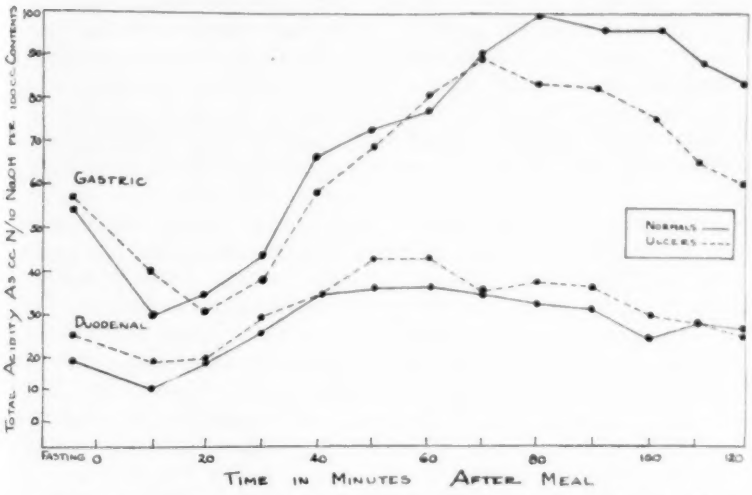

Chart 7.—Average total acidity of samples collected simultaneously from just above and just below the pylorus from patients with duodenal ulcer compared with that of samples collected from a group of normal subjects with gastric hyperacidity.

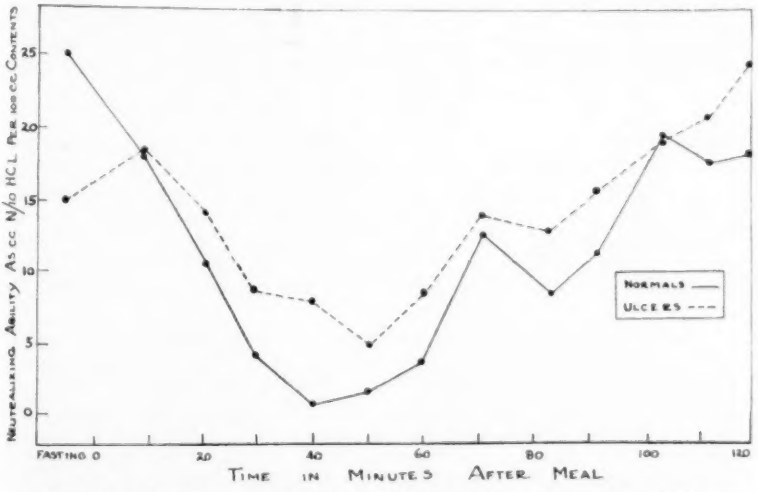

Chart 8.—Average excess neutralizing ability of the contents of the first part of the duodenum in patients with duodenal ulcer compared with that for a group of normal subjects with gastric hyperacidity.

which was noted in patients with ulcer but not in normal subjects (chart 1) is probably another manifestation of a defective neutralizing mechanism.[3e] In this respect, too, it is of interest that the average excess neutralizing ability of the duodenal contents (chart 8) was less in normal persons than in patients with ulcer. This fact, we assume, is attributable to a more efficient regulatory mechanism, which prevents wide excursions from the average in the direction either of excess acidity or of excess neutralizing ability.

It is to be emphasized that the conclusions we have drawn are all predicated on studies made on the acid concentration and not on the volume of gastric and duodenal contents. We have every reason to believe that the normal persons we selected were as much persons with hypersecretion as were the patients with duodenal ulcer, but with our method of study it was impossible to measure total amounts of acid without seriously interfering with normal physiologic processes.

The findings reported in this study are merely another small link in a growing chain of evidence indicating that the acid gastric juice per se is not so important a factor in ulcer as it has hitherto been considered. It is common knowledge that normal persons may have values for gastric acid just as high as patients with duodenal ulcer,[11] and it is just as well recognized that there is no reduction in gastric acidity with the healing of an uncomplicated duodenal ulcer.[12] Bloomfield and French [12b] could demonstrate no constant relationship between the basal gastric acidity and the speed of healing of an ulcer. Alvarez [12a] found no certain relationship between the acid titer and the intractability of an ulcer. Brown and Dolkart [12c] concluded that the trend of gastric acidity bears no relationship to the onset of a recurrence in patients with ulcer. Prolonged gastric hypersecretion in dogs has failed according to

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11. Baird, M. M.; Campbell, J. M. H., and Hern, J. R. B.: Gastric Secretion, Physique and Physical Fitness, Guy's Hosp. Rep. **74**:339, 1924. Bennett, T. I., and Ryle, J. A.: Studies in Gastric Secretion: V. A Study of the Normal Gastric Function Based on the Investigation of One Hundred Healthy Men by Means of the Fractional Method of Gastric Analysis, ibid. **71**:286, 1921. Polland, W. S., and Bloomfield, A. L.: Normal Standards of Gastric Function, J. Clin. Investigation **9**:651, 1931. Bloomfield.[2b] Bloomfield and Polland.[2d] Hurst.[2i] Rehfuss.[2l]

12. (*a*) Alvarez, W. C.: The Unreliability of Gastric Analysis as an Index to Prognosis in Cases of Peptic Ulcer, editorial, Am. J. Digest. Dis. **6**:557, 1939. (*b*) Bloomfield, A. L., and French, L. R.: Basal Gastric Secretion in Cases of Peptic Ulcer: Relation of Acidity to Healing of Ulcer, J. Clin. Investigation **17**:667, 1938. (*c*) Brown, C. F. G., and Dolkart, R. E.: Gastric Acid During Recurrences and Remissions of Duodenal Ulcer, Arch. Int. Med. **60**:680 (Oct.) 1937. (*d*) Sandweiss, D. J.; Sugarman, M. H.; Friedman, M. H. F.; Saltzstein, H. C., and Farbman, A. A.: The Effect of Urine Extracts on Peptic Ulcer: An Experimental and Clinical Study, Am. J. Digest. Dis. **8**:371, 1941. (*e*) Bockus, Glassmire and Bank.[2f] (*f*) Hurst and Venables.[2j]

some investigators,[13] to produce chronic gastric or duodenal ulcer, and we were able to demonstrate that even though temporary gastric hypersecretion in normal dogs frequently interferes with adequate neutralization in the duodenal bulb, the impairment is usually slight and for the most part is rapidly corrected.[14] What well might prove to be the death knell of the theory of the acid factor in ulcer is the recent work with urogastrone. This has shown rather conclusively that the urine of patients with symptoms of active duodenal ulcer contains a gastric secretory depressant [15] and, what is even more striking, that normal urine contains a substance having a definite prophylactic and therapeutic effect against Mann-Williamson ulcers and causing symptomatic improvement in patients with duodenal ulcer without bringing about any decrease in the gastric secretory response to stimuli.[12d]

There is much to corroborate the suggestive evidence we have gathered that a primary defect in duodenal ulcer is an impaired efficiency of duodenal neutralization. Resistance to the formation of an experimental ulcer has been shown to decrease in proportion to an interference with the alkalinizing mechanism of the duodenum.[8] A relative acid-alkali imbalance [4] and a relative deficiency of neutralizing and diluting fluid, as well as a disturbance in the neutralizing and diluting mechanism,[3c] have been demonstrated in patients with duodenal ulcer. There is some evidence, moreover, that the neutralizing juices, the pancreatic and the biliary in particular, are defective in such patients.[16]

It is difficult to conceive of immediate effective neutralization of gastric chyme as it enters the duodenum unless there is a considerable concentration of duodenal contents in the bulb. One of us (Thomas [17]) previously suggested that an interference with "receptive relaxation" in

13. Orndorff, J. R.; Bergh, G. S., and Ivy, A. C.: Peptic Ulcer and the "Anxiety Complex," Surg., Gynec. & Obst. **61**:162, 1935. Schmidt, C. R., and Fogelson, S. J.: The Effect of Physiologic Hypersecretion on the Gastro-Duodenal Mucosa, Am. J. Physiol. **120**:87, 1937.

14. Berk, J. E.; Thomas, J. E., and Rehfuss, M. E.: The Effect of Gastric Hypersecretion on the Reaction and Neutralizing Ability of the Contents of the First Part of the Duodenum in Normal Dogs, Am. J. Digest. Dis. **9**:297, 1942.

15. Friedman, M. H. F., and Sandweiss, D. J.: The Gastric Secretory Depressant in Urine, Am. J. Digest. Dis. **8**:366, 1941.

16. Ask-Upmark, E.: Further Observations on the Pathogenesis of Peptic Ulcer, Acta med. Scandinav. **103**:280, 1940. Ivy, A. C.; Schrager, U. G., and Morgan, J. E.: Spontaneous Ulcers in Dogs with Chronic Mild Icterus, Proc. Soc. Exper. Biol. & Med. **30**:698, 1933. Jergesen, F. H., and Simonds, J. P.: The Blood Lipase in Patients with Peptic Ulcer, J. Lab. & Clin. Med. **19**:1054, 1934. McClure, C. W., and Huntzinger, M. E.: Pathologic-Physiologic Studies on Changes in the External Secretions of the Pancreas and Liver, New England J. Med. **206**:507, 1932. Reymont, A.: A Study of Liver Function in Experimental "Peptic" Ulcer, Am. J. Digest. Dis. **7**:65, 1940.

17. Thomas, J. E.: The Maximal Acidity of the Intestinal Contents During Digestion, Am. J. Digest. Dis. **7**:195, 1940.

the duodenum of patients with ulcer, either as a result of changes in the duodenum before the appearance of ulceration or as a result of the ulcer itself, might act to prevent an accumulation of duodenal contents in the juxtapyloric region. The retention of this neurophysiologic mechanism in normal persons and its disruption in patients with ulcer might help explain the more efficient duodenal neutralization in the former. Morton [4] earlier was led to believe from his experimental work that a basic defect in patients with ulcer is some derangement in the function of the pylorus which results in improper mixing of the gastric and the duodenal contents.

Attention was called to the relative independence of the graphic curves of titratable gastric acidity and of gastric p_H and to the lack of close parallelism between the several indexes of gastric acidity and the p_H in the duodenal cap. It seems justifiable to conclude that none of the customary measures of gastric acidity can be relied on with any certainty to indicate the behavior of the effective acidity (p_H) present over the same period of time in the duodenal bulb.

SUMMARY AND CONCLUSIONS

1. The contents of the duodenal bulb, which is the parent site of most clinical ulcers, are more acid in patients with duodenal ulcer than in normal subjects. In patients with ulcer after an Ewald meal the contents of the duodenal bulb have an average p_H of about 3.9.

2. The ability of the contents of the first part of the duodenum to neutralize, buffer and dilute the gastric chyme is in evidence in patients with duodenal ulcer although impaired. In contrast to that of normal persons, however, the neutralizing ability of the duodenal bulb contents is overcome more frequently, to a greater extent and for longer periods of time.

3. Free acid is more frequently encountered in the contents of the first part of the duodenum in patients with an ulcer in that location than it is in normal subjects.

4. Patients with duodenal ulcer appear to differ from normal persons not only in the direction of gastric hyperacidity but in the direction of a defectiveness of the neutralizing capacity in the duodenal bulb.

5. Acid gastric juice per se is not so important a factor in duodenal ulcer as it has hitherto been considered.

6. The degree of acidity of the stomach contents is by no means the sole determinant of the degree of acidity of the duodenal bulb contents. There is no parallel relationship between the effective acidity (p_H) in the duodenal bulb and any of the customary indexes of gastric acidity.

Dr. B. B. Vincent Lyon permitted study of the patients and use of the facilities of the gastrointestinal disease clinic, and Dr. Melvin Dillman and Dr. Karl Kornblum cooperated in performing the roentgenologic studies on each subject.

MERCURIAL AND XANTHINE DIURETICS IN CHRONIC CONGESTIVE HEART FAILURE

A COMPARATIVE SURVEY

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CLEVELAND

The present study was made possible by employing directly the daily weight of patients with cardiac disease—the simplest and yet most accurate means of following diuretic response, great or small. A number of the commonly used diuretics were administered to these patients, including some of the more recently popularized agents which contain the combination of a xanthine derivative with a mercurial.

Before going into further details we would stress two points which seem to us of importance in consideration of previous studies on diuretics. First, most of the observations up to the present have necessarily been of relatively short duration (usually a matter of weeks) because of the time limitations placed on the hospitalization of all types of patients. Marvin,[1] in his studies on xanthine derivatives, emphasized the fact that his patients were under observation from only three weeks to a little over six weeks. The patients in our series were under continuous observation for an average of over forty-two weeks, because of favorable circumstances of hospitalization. Second, the evaluation of diuretic action has usually been derived from observations made on patients with far advanced congestive heart failure. It is logical to presume that in the presence of a great excess of edema fluid any one of many diuretics might conceivably produce a satisfactory response. This response, however, has been shown to vary in relation to known factors, such as digitalization and excess or deficiency of chloride ions or sodium ions.[2] It is our opinion that until these factors become

1. Marvin, H. M.: The Value of the Xanthine Diuretics in Congestive Heart Failure, J. A. M. A. **87**:2043 (Sept. 25) 1926.

2. (*a*) Keith, N. M., and Whelan, M.: A Study of the Action of Ammonium Chloride and Organic Mercury Compounds, J. Clin. Investigation **3**:149, 1926. (*b*) Blumgart, H. L.; Gilligan, D.; Levy, R. C., and Brown, M. G.: The Effects

(Footnote continued on next page)

stabilized, any accurate survey of diuretic action must be open to question.

The present work has been restricted to the use of diuretics in 16 patients who were followed during a period which ranged from three weeks to one hundred and twelve weeks. Initially, of course, each patient had been in a state of advanced congestive heart failure. Furthermore, the condition of each patient was first controlled by the use of digitalis, ammonium salts and mercurial diuretics until all gross evidence of clinical edema was either entirely absent or minimal to the extent that the administration of a diuretic did not produce any further conspicuous drop in the average weight level of the patient, as could be seen on the daily weight chart. This state we have conveniently designated the "state of balance" (fig. 1). Figure 1 demonstrates clearly that if a given patient has received a series of injections of

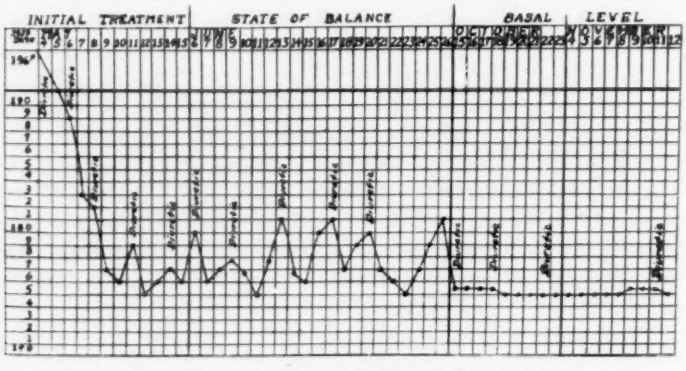

Fig. 1.—Weight chart of a patient with hydropic cardiac disease, showing achievement of a "state of balance," a condition in which the administration of a diuretic will not produce any further conspicuous drop in the average weight level.

mersalyl solution (2 cc.) at any chosen interval (e. g., four days apart) and the average resultant loss of weight recorded on the chart indicates that a uniform diuretic response is being obtained from these successive treatments, it can be considered that this patient has reached a "state of balance." This so-called "state of balance" must not be confused with the "basal level," or edema-free state, in which a diuretic is no longer capable of producing a response as indicated by the weight chart

of Diuretics on Water and Salt Metabolism, Tr. A. Am. Physicians **47**:304, 1932. (*c*) Ethridge, C. B.; Myers, D. W., and Fulton, M. N.: Modifying Effect of Various Inorganic Salts on Diuretic Action, Arch. Int. Med. **57**:714 (April) 1936. (*d*) Herrmann, G., and Decherd, G. M., Jr.: Further Studies on the Mechanism of Diuresis with Especial Reference to the Action of Some of the Newer Diuretics, J. Lab. & Clin. Med. **22**:767, 1937.

(see right side of figure 1). This point will be taken up more fully in a future publication.

We hoped that for a given agent the average of any three or four successive diuretic effects obtained during such a "state of balance" could be considered to be a more or less typical response for that drug at the selected dose. A different diuretic or a different dose of the first diuretic could then be given at the same interval, so that the two responses could be compared directly. In this way the average loss in weight could be assumed to be an accurate index of the diuretic comparability of any two drugs in a given patient. In order to be sure that the patient continued to respond to the same degree as before, a period of observation with the original drug at its first dose followed the trial of the second diuretic or the second dose, so that once again a direct comparison was obtained.

The diuretic effects which were noted in these patients before the establishment of this control period, i. e., "state of balance," have been omitted from this survey because the value of these observations was mitigated by some of the objections just mentioned. Hence, of a total of six hundred and ninety-three separate injections of the various diuretics which were administered to these 16 patients, the results from but two hundred and seventy-eight injections were considered sufficient to serve as an accurate index of the diuretic response.

In checking the literature it was noted that in some of the experimental studies on the effect of diuretics on animals a pattern somewhat similar to that adopted here was followed.[3] For instance, Bliss and Morrison [4] stated: "It should be understood that the drugs were not administered until long observation had established that the rabbits were in good balance as determined by intake, output and weight."

At the inception of this study mersalyl solution (2 cc.) was routinely employed in all cases. Occasionally, in cases in which the edema was refractory, a trial of mersalyl solution in a larger dose (4 cc.) was dared in hopes of a better response. However, anxiety over the possible toxic effects prompted the acceptance of the suggestion of Swigert and Fitz [5] that a smoother diuresis can be obtained when a mercurial diuretic is given in smaller and more frequent doses. Accordingly, in some cases

3. (*a*) DeGraff, A. C.; Batterman, R. C., and Lehman, R. A.: Influence of Theophylline upon Absorption of Mercupurin (Novurit) and Salyrgan (Mercury Preparations) from Site of Intramuscular Injection, J. Pharmacol. & Exper. Therap. **62**:26, 1938. (*b*) DeGraff, A. C.; Batterman, R. C.; Lehman, R. A., and Yasuna, E.: Excretion of Mercury Following Administration of Mercurial Diuretics With and Without Theophylline, Proc. Soc. Exper. Biol. & Med. **39**: 250, 1938. (*c*) Ethridge, Myers and Fulton.[2c]

4. Bliss, A. R., and Morrison, R. W.: A Comparative Study of Certain Xanthine Diuretics, J. Tennessee M. A. **25**:387, 1932.

5. Swigert, V. W., and Fitz, R.: The Effect of Mersalyl (Salyrgan) on Plasma Volume, J. A. M. A. **115**:1786 (Nov. 23) 1940.

mersalyl solution was injected in doses of 1 cc. and even in doses as low as 0.5 cc. In many instances we administered some of the newer diuretics, such as mersalyl-theophylline solution (2 cc.), by injection and also orally and rectally. Finally, mersalyl solution combined with theophylline with ethylenediamine (7½ grains [0.5 Gm.]) and theophylline with ethylenediamine alone (7½ grains) were employed.

RESULTS

In the construction of figure 2 the average loss of weight from the use of a given diuretic was compared in each patient with the average loss of weight following each of the other diuretics. The comparative effect of each diuretic which is represented on the chart does not indicate the actual total average diuresis (loss of weight) but demonstrates the relative efficiency of each drug compared with the other diuretics studied. All these calculations are based on the average loss of weight. The maximum diuretic response (in pounds) is represented in each patient by 100 per cent, so that a score of 100 indicates that a given agent produced a diuretic response as high as or higher than that of each of the other drugs in every case in which it was used (fig. 2).

The maximum diuretic effect in this group was obtained by somewhat varying modes of administration. It was found that an equal diuretic effect (100 per cent) was produced, first, by administering mersalyl solution in one large dose of 4 cc. and, second, by giving a 1 cc. dose of mersalyl solution one hour after an injection of theophylline with ethylenediamine (7½ grains). It may be of interest to note that the greatly enhanced diuretic effect from the latter method of administration was accidentally discovered in a patient who had been given theophylline with ethylenediamine (7½ grains intravenously) during an attack of paroxysmal dyspnea. By chance he was given the routine dose of mersalyl solution (1 cc. intramuscularly) one hour later. The loss of weight noted on his chart the next day revealed an unusual degree of diuresis. During subsequent observations the same effect was confirmed in this patient and in others. In each case, as can be seen on the chart (fig. 2), this method produced the greatest degree of diuresis. As a natural sequence the same combination of drugs, viz. mersalyl solution (1 cc.) and theophylline with ethylenediamine (7½ grains), was administered simultaneously in one syringe, but it did not produce as great a degree of diuresis as that resulting when the drugs were given one hour apart (fig. 2). An increased dose of mersalyl solution (2 cc.) failed to alter this result. In fact, the results obtained from the simultaneous injections (65.2 per cent) were not so great as the diuretic effect produced by mersalyl solution in 2 cc. doses alone (87.7 per cent), though they were superior to the diuresis produced by mersalyl solution in doses of 1 cc. (58 per cent).

Although the effect of mersalyl solution in high doses (4 cc.) is as great as the diuretic response obtained from mersalyl solution (1 cc.) and theophylline with ethylenediamine (7½ grains) given in separate injections (100 per cent), the obvious difference in the quantity of mercury in the two doses (4:1) undoubtedly makes the frequent use of mersalyl solution in such a great dose hazardous. In fact, according to the work of Barbour [6] on rabbits and that of Johnstone and Keith [7]

100
Theophylline with ethylenediamine (7½ grains) followed after one hour by mersalyl solution (40 mg. Hg) 1 cc.
100
Mersalyl solution (160 mg. Hg) 4 cc.
87.7
Mersalyl solution (80 mg. Hg) 2 cc.
65.2
Mersalyl solution (40 mg. Hg) 1 cc. administered simultaneously with theophylline with ethylenediamine (7½ grains)
62.5
Mersalyl solution (80 mg. Hg.) 2 cc. administered simultaneously with theophylline with ethylenediamine (7½ grains)
58.0
Mersalyl-theophylline solution (40 mg. Hg; 1½ grains of theophylline) 2 cc.
57.7
Mersalyl solution (40 mg. Hg) 1 cc.
32.0
Mersalyl solution (20 mg. Hg) 0.5 cc.
29.9
Theophylline with ethylenediamine (7½ grains)
25.1
Mersalyl solution (80 mg. Hg) with theophylline (40 mg.) given orally; also mersalyl solution (160 mg. Hg.) with theophylline (157 mg.) given rectally.

Fig. 2.—Comparison of the relative efficiency of the diuretics studied. A score of 100 per cent indicates that a given agent produced a diuretic response as high as or higher than that of each of the other drugs in every case in which it was used.

6. Barbour, H. G.: Mercuric Chloride Poisoning in Animals Treated Unsuccessfully by Parenteral Administration of Hall's New Antidote, J. A. M. A. **64**:736 (Feb. 27) 1915.

7. Johnstone, B. I., and Keith, H. M.: Toxicity of Novasurol (Merbaphen): Its Action on the Kidney of the Rabbit, Arch. Int. Med. **42**:189 (Aug.) 1928. Keith, H. M., and Johnstone, B. I.: The Action of Merbaphen (Novasurol) on the Kidney of the Dog: A Combined Functional and Pathologic Study, ibid. **44**:438 (Sept.) 1929.

on dogs, the lethal dose of merbaphen for a man weighing 70 Kg. was theoretically calculated to be 6 cc. of a 10 per cent solution.

In order to clarify the representation of these diuretics on the chart, which is on a percentage basis, a few examples of actual average loss of weight per injection are cited. Mersalyl solution (1 cc.) injected intramuscularly one hour after the intravenous administration of theophylline with ethylenediamine (7½ grains) produced an average loss of weight of 5.9 pounds (2.6 Kg.), as against a loss of 3.1 pounds (1.4 Kg.) produced by mersalyl solution (1 cc.) alone or a loss of 3.5 pounds (1.6 Kg.) produced by mersalyl solution (1 cc.) and theophylline with ethylenediamine (7½ grains) given simultaneously.

It should be emphasized that the "state of balance" which has been selected for this group of patients has set up a critical test for any given diuretic. Whereas reports in the literature [8] indicated excellent diuretic results from oral and from rectal administration of mersalyl solution and mersalyl-theophylline solution, the results from the use of these agents in this survey can be considered negligible (25 per cent). We believe that a logical explanation for the favorable results reported may lie chiefly in the practice of evaluating diuretic results in patients with a large accumulation of edema. In our patients the use of theophylline with ethylenediamine (7½ grains) intravenously almost invariably failed to produce a diuretic response of any consequence (30 per cent). This seems to indicate that in this group of patients, in whom a relatively small quantity of edema remained, theophylline with ethylenediamine had no direct diuretic action; yet in conjunction with mersalyl solution, which by itself was capable of producing a good diuresis in these very same patients, theophylline with ethylenediamine actually enhanced the diuretic effect of mersalyl solution.

It can readily be seen on the chart that mersalyl-theophylline solution (2 cc.), which at this time is the only commercially available preparation containing mersalyl, produced a decidedly inferior diuretic response in this group of patients (3.03 pounds [1.3 Kg.] per injection). In fact, although this solution was given in a 2 cc. dose, the result produced (58

8. Fulton, M. N.: Mercurin Suppositories as a Diuretic in the Treatment of Edema, New England J. Med. **214**:1092, 1936. Parkinson, J., and Thomson, W. A. R.: A Mercurial (Novurit) Suppository as a Diuretic for Cardiac Edema, Lancet **1**:16, 1936. Brightman, I. J., and Batterman, R. C.: The Treatment of Edema by Rectal Administration of Diuretics, J. Lab. & Clin. Med. **25**:1038, 1940. Brightman, I. J., and Lehman, R. A.: Experimental Study of Rectal Administration of Mercurial Diuretics (in Suppositories), ibid. **25**:56, 1939. Blackford, L. M.: Salyrgan-Theophylline by Mouth, Case of Congestive Heart Failure, J. M. A. Georgia **29**:397, 1940. Claiborne, T. S., and Logue, R. B.: Use of Salyrgan-Theophylline Suppositories in Congestive Heart Failure, ibid. **29**:399, 1940. Flexner, J.: Mercurial Suppository as a Diuretic, Ann. Int. Med. **11**:1962, 1938. Ethridge, Myers and Fulton.[2c] Herrmann and Decherd.[2d]

per cent) merely equals that produced by mersalyl solution given alone in a 1 cc. dose (57.7 per cent).

For some time we have been at a loss to explain this puzzling clinical phenomenon. However, the clinical observations of Wermer and Zak (1925),[9] confirmed in 1926 by the experimental work of Fröhlich and Zak,[10] demonstrated that xanthines increased the permeability of the body tissues. In 1938 DeGraff, Batterman and Lehman [8a] showed conclusively that both mercupurin and mersalyl solution with theophylline are absorbed almost completely within one hour after intramuscular injection and proved that the presence of theophylline influences the absorption of these mercurial diuretics to a marked extent. The same workers with an associate [8b] further proved that theophylline greatly increased the rate of urinary excretion of mercury after the injection of mercurin or mersalyl solution. The amount of mercury which ordinarily is excreted within six hours was increased 30 to 40 per cent after intravenous injection and 100 to 300 per cent after intramuscular injection.

Hence, despite the fact that the effect of the mercurials may be enhanced by the more rapid absorption brought about by the use of theophylline, the final effect as shown in this survey seems to indicate that the more rapid rate of excretion of mercury which follows actually tends to shorten the period of diuresis. Thus, the action of theophylline, which at first glance may serve as a most useful adjunct in hastening the absorption of the mercurials, seems to have its beneficial action in respect to absorption more than neutralized by an action in which it hastens excretion of the mercury through the urinary tract. Yet this does not explain the superlative diuretic effect obtained when mersalyl solution (1 cc.) is given separately, viz. one hour after the injection of theophylline with ethylenediamine (7½ grains). This last question must remain unanswered for the present.

SUMMARY

It is proposed that accurate clinical methods for the evaluation of mercurial and xanthine diuretics in patients with hydropic cardiac disease require a preliminary period of treatment until all grossly visible edema has disappeared. This disappearance has been determined from the strict use of the daily weight of the patient, and the resultant condition has been called by us a "state of balance."

In patients in this "state of balance" only the really effective diuretics are capable of producing a further diuresis.

9. Wermer, P., and Zak, E.: Klinische Studien über die Wirkung von Diuretics auf Gewebe, Wien. klin. Wchnschr. **38**:1177, 1925.

10. Fröhlich, A., and Zak, E.: Ueber medikamentöse Beeinflussung der Gewebsdurchlässigkeit, Wien. med. Wchnschr. **39**:493, 1926.

The following observations were made on 16 patients given a total of two hundred and seventy-eight injections:

1. Injectable preparations in which mersalyl solution was combined with theophylline or theophylline with ethylenediamine were notably less efficient than pure mersalyl solution administered in similar doses.
2. Oral and rectal modes of therapy which employed combinations of mersalyl solution and theophylline produced little diuretic effect compared with that produced by injectable preparations administered to the same patients.
3. Theophylline with ethylenediamine (7½ grains) given intravenously to patients in a "state of balance" did not produce any evident diuresis by itself.
4. Finally, the greatest diuresis was produced by mersalyl solution (1 cc.) given intramuscularly one hour after intravenous administration of theophylline with ethylenediamine (7½ grains). A superior degree of diuresis resulted, which was equaled only by a dose of mersalyl solution alone containing four times as much mercury, namely, 4 cc.

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HYPERACTIVE VASODEPRESSOR CAROTID SINUS REFLEX

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BROOKLYN

It has been demonstrated in recent years that blood pressure is automatically regulated by alterations in the intra-arterial pressure. This automatic regulation is maintained by a system of pressoreceptor innervations localized in different areas of the vascular tree. The most important areas of such innervations are in the aorta and, especially, in the carotid sinus regions.

Because the carotid sinus regions have easily accessible nerve terminals and because they contain the most active pressoreceptors, these areas in man have been subjected to considerable investigation in recent years.

It was the illuminating experimental work of Hering [1] which first demonstrated the presence of nerve connections between the carotid sinus regions and the medullary centers. He [2] was also the first to demonstrate the occurrence of a drop in pressure on stimulation of the carotid sinus.

Hering found that in the adventitial coat of the pouched-out area of the internal carotid artery, at its junction with the external carotid, there are present sensory receptor end organs which terminate in characteristic menisci and emerge as spiral fibers which form the sinus nerve, bearing his name. The sinus nerve merges with the glossopharyngeal nerve, which reaches the medulla. According to Braucker,[3] in some animals afferent tracts from the carotid sinus region are found also in the vagus, the cervical sympathetic and the hypoglossal nerves, and the end organs of such tracts are not confined strictly to the carotid sinus but are found also in the adjacent portion of the common and the external carotid artery.

From the Cardiologic Service, Department of Medicine, Coney Island Hospital and Harbor Hospital.

1. Hering, H. E.: Der Karotisdruckversuch, München. med. Wchnschr. **70**: 1287, 1923.

2. Hering, H. E.: Die Karotissinusreflexe auf Herz und Gefässe, Dresden, Theodor Steinkopff, 1927.

3. Brauecker, W.: Das pressorezeptorische Nervensystem und seine praktische Bedeutung in der Chirurgie, Beitr. z. klin. Chir. **158**:309, 1933.

In the medulla the afferent fibers make synaptic connections at the various areas, or so-called "centers," with the efferent neurons which run in the sympathetic, vagal and respiratory nerve systems and which control the vasomotor tone throughout the body, the heart rate and the respiration. There are also synaptic connections of the afferent tracts from the carotid sinus with other regions of the brain, resulting in various other manifestations. These will be left out of the present discussion.

Under normal conditions the carotid sinuses, together with the aortic depressor nerves, control the circulation by impulses set up as a result of arterial pressure changes within the vessels. A sudden spontaneous increase in pressure stimulates the receptor organs in these locations and sets up afferent impulses which enter the medullary region and result in vasodepression, cardioinhibition, some alteration in respiration, a decrease in the secretion of epinephrine, and so on, all of which result in a lowering of the blood pressure and slowing of the heart. A decrease in the intra-arterial pressure produces the opposite effects.

The sinus nerves have a natural tonus which helps maintain the blood pressure and the cardiac rate at certain levels at all times. This is shown by the fact that if both nerves are cut some rise in pressure and acceleration of the heart will result. Basing his theory on these facts, Hering [4] postulated the possibility that essential hypertension might be due to absence of the depressor reflex of the carotid arteries and of the aorta. Koch and Mies [5] and Heymans and Bouckaert [6] produced prolonged hypertension by bilateral denervation of the carotid sinus and section of the aortic depressor nerves. Their finding was corroborated by Nowak and Walker,[7] who produced hypertension which lasted about three years.

At the present writing the question as to how much of a role the absence or the diminution of the activity of the sinus and the aortic nerves plays in the pathogenesis of hypertension has not been answered. Heymans, Bouckaert and Regniers [8] in a complete review of the subject

4. Hering, H. E.: Die klinische Bedeutung der Carotissinusreflexe, Med. Klin. **23**:155, 1927.

5. Koch, E., and Mies, H.: Chronischer arterieller Hochdruch durch Dauerausschaltung der Blutdruckzügler, Krankheitsforschung **7**:241, 1929.

6. Heymans, C., and Bouckaert, J. J.: Observations chez le chien en hypertension artérielle chronique et expérimentale, Compt. rend. Soc. de biol. **106**:471, 1931.

7. Nowak, B. I., and Walker, I. J.: Experimental Studies Concerning the Nature of Hypertension, New England J. Med. **220**:269, 1939.

8. Heymans, C.; Bouckaert, J. J., and Regniers, P.: Le sinus carotidien et la zone homologue cardio-aortique, Paris, Gaston Doin & Cie, 1933.

up to 1933 expressed the opinion that it plays a part in most cases. In some cases the sensitivity of the vasomotor center to such factors as carbon dioxide, increased hydrogen ion concentration (which may also act reflexly on the center) and ischemia is the cause. In others, those of the so-called "white hypertensives," to quote Volhard, some humoral substance freed from the kidney is responsible. In some cases all these factors may be at play.

More recently, since the work of Goldblatt and co-workers,[9] the theory of the renal origin of hypertension has assumed the greatest prominence. It is applied not merely to the "white hypertensives" of Volhard but to essential hypertension as well.

If hypertension is caused by the absence or diminution of activity of the carotid sinus reflex, hypertensive patients theoretically should show little or no drop in pressure on stimulation of the carotid sinus. This has not been found to be the case. On the contrary, Koch [10] in testing 50 subjects found that a drop in pressure occurs more frequently in hypertensive than in normal persons. He and Hering also observed that the drop in pressure is not always caused by slowing of the heart, which occurs at the same time, for by injection of atropine sulfate the cardioinhibitory reflex may be abolished, while a drop in pressure will still occur on carotid sinus stimulation. This observation was also made by Weiss and Baker,[11] Mandelstamm and Lifschitz [12] and other authors.

To explain the occurrence of an accentuated vasodepressor reflex in cases in which it should actually be absent, Heymans and co-workers as well as Hering and other authors postulated the theory that in such cases the pressoreceptor terminals in the adventitia become insensitive to changes in intrasinal pressure, which results in hypertension. On the other hand, the same terminals become more sensitive to external compression because of sclerosis of the carotid arteries. For this reason, vasodepression occurs more frequently in carotid artery sclerosis associated with hypertension.

Comparatively small series of clinical cases in which the vasodepressor effect of the carotid sinus reflex has been studied are recorded in the literature. For this reason the following study of 700 cases in

9. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. N.: The Production of Persistent Hypertension in Dogs, Am. J. Path. **9**:942, 1933.

10. Koch, E.: Ueber den depressorischen Gefässreflexe beim Karotisdruckversuche am Menschen, München. med. Wchnschr. **71**:704, 1924.

11. Weiss, S., and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease: Its Role in Causation of Fainting and Convulsions, Medicine **12**:298, 1933.

12. Mandelstamm, M., and Lifschitz, S.: Die Wirkung der Karotismusreflexe auf den Blutdruck beim Menschen, Arch. f. inn. Med. **22**:397, 1932.

which the test was carried out is recorded. The study includes an analysis of the frequency and the degree of occurrence of this reflex in the two sexes, at various ages and at various levels of blood pressure. A comparative study was also made of the frequency and the degree of cardioinhibition in relation to vasodepression.

MATERIAL AND METHOD OF STUDY

The patients studied were ambulatory office patients. Most of them presented evidence of some degree of cardiovascular disease. Many, however, were free from such disease.

The patients were divided into four groups. In group I were placed persons whose blood pressure was within the normal range, being less than 150 systolic and 90 diastolic; in group II, patients with low grade hypertension, the systolic pressure ranging between 151 and 175 and the diastolic between 91 and 105; in group III, patients with moderate hypertension, the systolic pressure being between 176 and 200 and the diastolic between 105 and 125, and in group IV, patients with marked hypertension, the systolic pressure being over 220 and the diastolic over 125.

In each case the heart rate and the blood pressure were determined just before the test was done. In many cases in which there was a pronounced spontaneous fluctuation in blood pressure, described in a previous communication,[13] two or three determinations were done before the test, and the lowest reading was used for comparison.

The test was performed with the patient in the sitting posture. Gradual pressure was applied first to the right carotid sinus region, and the results recorded, and then to the left carotid sinus region. If the patient exhibited marked cardioinhibition with stoppage of the heart, the stimulation was discontinued momentarily and then continued in gradual stages. I found that with this procedure, cardioinhibition if not extreme would soon subside, and the heart rate would return to normal or even accelerate. The blood pressure, however, would drop to its lowest level later, on continued carotid sinus stimulation. The object of abolishing cardioinhibition was to eliminate the factor of slowing or stoppage of the heart itself as a possible cause for the fall in pressure.

The lower of the two readings of the blood pressure, obtained on stimulation of the right or of the left carotid sinus, was used for comparison with the original reading, obtained just before the test was performed, and the percentage difference calculated.

The patients were divided into groups according to sex and again according to age. The degree of cardioinhibition was designated by plus marks as follows: 1 plus if slowing was less than 10 per cent of the original rate, 2 plus for 10 to 30 per cent slowing, 3 plus for 30 to 70 per cent slowing and 4 plus for stoppage of the heart for at least three seconds. If no slowing occurred the designation was a zero mark. The findings are shown in the accompanying tables and charts.

ANALYSIS OF FINDINGS

General Observations.—The effects of stimulation of the carotid sinus were slowing or stoppage of the heart, a drop in pressure and various cerebral and other manifestations described by previous authors, notably Weiss

13. Sigler, L. H.: Spontaneous Nonrhythmic Variations in the Blood-Pressure Levels and in the "Silent Gap," Am. J. M. Sc. **177**:494, 1929.

and Baker [11] and Ferris, Capps and Weiss.[14] There was a pronounced variation in the incidence and in the degree of response of each of these components of the reflex. Some patients showed only, or mainly, a greater or less degree of cardioinhibition, others vasodepression and still others cerebral or other manifestations. There was also a decided difference in response on stimulation of the two carotid sinuses. Thus in some patients there was marked cardioinhibition with no drop in pressure or other manifestations with stimulation on one side and no cardioinhibition but a pronounced drop in pressure with stimulation on the other side, and so on.

The response varied to some extent with the position of the patient. A greater response usually occurred with the patient in the upright posture than with him in the dorsal recumbent position.

Cardioinhibition if present occurred before any other manifestations. The percentage of patients showing cardioinhibition in this series was about the same as in my series previously reported.[15] If a drop in blood pressure occurred, it commenced soon after stimulation started, and the maximum drop would develop in four to fifty seconds. The force and the duration of stimulation necessary to accomplish the maximum drop in pressure varied with different patients. The blood pressure returned to the original level in one-half to three minutes after stimulation was discontinued. Regniers [16] found the maximum duration of the drop in pressure after stimulation was stopped to be about two minutes.

In those patients who presented other manifestations of the reflex, such as dizziness, fainting, unconsciousness or the milder disturbances, such manifestations would occur at about the time when the blood pressure reached its lowest level or a little later.

Patients who presented marked cardioinhibition had, of course, a drop in pressure as a result of slowing or stoppage of the heart. In many the pressure would return to nearly the original level after cardioinhibition subsided, and on continuation of the stimulation the blood pressure would again drop. When a patient exhibited dangerous

14. Ferris, E. B.; Capps, R. B., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions, Medicine **14**:377, 1935.

15. Sigler, L. H.: Clinical Observations on the Carotid Sinus Reflex: I. The Frequency and the Degree of Response to Carotid Sinus Pressure Under Various Disease States, Am. J. M. Sc. **186**:110, 1933; II. The Response to Carotid Sinus Pressure at Various Ages and Heart Rates and Rhythms, ibid. **186**:118, 1933; Further Observations on the Carotid Sinus Reflex, Ann. Int. Med. **9**:1380, 1936; Hyperactive Cardioinhibitory Carotid Sinus Reflex: A Possible Aid in the Diagnosis of Coronary Disease, Arch. Int. Med. **67**:177 (Jan.) 1941.

16. Regniers, P.: Le sinus carotidien en clinque, Rev. belge d. sc. méd. **2**:207, 1930.

cerebral manifestations, the stimulation had to be discontinued before the lowest blood pressure was obtained.

Compressing the common carotid arteries below the bifurcation resulted in a rise in pressure in many of the normal and hypertensive subjects. This observation corroborates the findings of Gammon.[17]

The Incidence and Degree of Response in the Various Blood Pressure Groups, in the Two Sexes.—Of the 700 patients, 447 were males and 253 females. Of these, 393 males and 203 females showed a drop in blood pressure on stimulation of the carotid sinus. The balance, 54 males and 44 females, did not show any drop. Of this balance, 33 patients showed a rise in pressure. An occasional rise in pressure instead of a drop

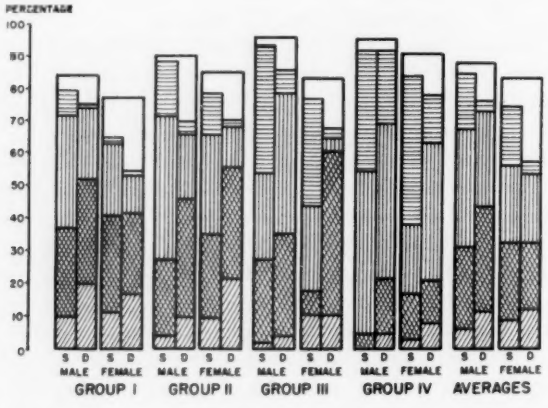

Fig. 1.—The incidence and the degree of drop in blood pressure on stimulation of the carotid sinus in 700 patients, expressed in the percentage of patients responding among males and among females in the four groups designated in table 1. Each whole bar represents the total number of patients responding. Each longitudinal semibar represents a systolic (*S*) or a diastolic (*D*) response. In the subdivisions of a semibar the degree of drop in blood pressure is represented as follows: less than 10 mm., diagonal lines; 10 to 25 mm., crosshatching; 25 to 50 mm., vertical lines, and over 50 mm., horizontal lines.

was also observed by Danielopolu and Radovici,[18] Marinesco and Kreindler [19] and other observers.

17. Gammon, G. D.: The Carotid Sinus Reflex in Patients with Hypertension, J. Clin. Investigation **15**:153, 1936.

18. Danielopolu, V., and Radovici, A.: Bewegungen des Unterkörpers, hervorgerufen durch der peripheren Vagusender, nach Durchschneidung des Rückenmarkes, Klin. Wchnschr. **6**:942, 1927.

19. Marinesco, G.; Kreindler, A., and Bruch, A.: Weitere Beiträge zum Studium der Reflexe des Sinus Caroticus in der Epilepsie, Ztschr. f. d. ges. exper. Med. **79**:333, 1931.

TABLE 1.—*Incidence and Degeree of Drop in Blood Pressure on Stimulation of the Carotid Sinus Among Males and Females Divided in Four Groups According to Blood Pressure* *

Blood Pressure Group	Total Number of Patients		Incidence of Drop in Blood Pressure					Degree of Drop in Blood Pressure												
			Male		Female			Male		Female		Less Than 10 Mm.				10-25 Mm.				25-50 Mm.				Over 50 Mm.			
												Male		Female		Male		Female		Male		Female		Male		Female	
	Male	Female	No.	%	No.	%		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
I	242	87	203	83.9	67	77.0	Systolic	192	79.3	55	63.2	21	9.9	9	10.3	66	27.3	26	29.8	86	35.5	19	21.8	19	7.9	1	1.1
							Diastolic	182	75.2	47	54.0	48	19.9	14	16.0	80	31.8	22	25.3	54	22.3	10	11.4	1	0.4	1	1.1
II	122	85	111	90.0	72	84.7	Systolic	108	88.5	65	76.4	4	3.2	8	9.4	30	24.5	22	25.8	52	42.6	26	30.5	22	18.0	9	10.5
							Diastolic	99	81.1	60	70.6	16	9.9	18	21.1	43	35.2	30	35.1	36	21.1	11	12.9	4	3.2	1	1.1
III	60	40	57	95.0	33	82.5	Systolic	56	92.2	31	77.5	1	1.6	4	10.0	13	21.6	3	7.5	15	25.0	10	25.0	27	45.0	14	35.0
							Diastolic	52	86.6	27	67.5	2	3.3	4	10.0	19	31.6	5	12.5	26	43.3	15	37.5	5	8.3	3	7.5
IV	23	41	22	95.6	37	90.2	Systolic	21	91.3	36	87.7	0	0.0	1	2.4	1	4.3	6	14.6	11	47.8	10	21.4	9	39.1	19	46.3
							Diastolic	20	86.9	32	78.1	1	4.3	3	7.3	4	17.3	6	14.6	11	47.8	17	41.4	5	21.7	6	14.6
Total	447	253	393	87.9	209	82.6	Systolic	379	82.5	187	73.9	26	5.8	22	8.7	112	25.1	57	22.5	164	36.6	65	25.6	77	17.2	43	17.0
							Diastolic	353	78.9	166	71.2	67	10.4	39	11.4	146	32.6	63	20.9	127	28.4	53	20.9	14	3.1	10	3.9

* Group I, normal blood pressure, less than 150 mm. systolic and 90 mm. diastolic; group II, low grade hypertension, pressures of 151 to 175 mm. systolic and 91 to 105 mm. diastolic; group III, moderate hypertension, pressures of 176 to 200 mm. systolic and 105 to 125 mm. diastolic, and group IV, marked hypertension, pressures over 200 mm. systolic and over 125 mm. diastolic.

Table 1 and figure 1 show the incidence and the degree of drop in pressure on stimulation of the carotid sinus in the two sexes and in each of the blood pressure groups as well as the total for all groups. Most subjects responding had a drop in both the systolic and the diastolic pressure. In some, however, there was a drop either in the systolic or in the diastolic pressure alone.

It will be noted that the incidence of response was relatively greater in males than in females. This variation was also observed by Koch.[10] Instead of no drop or a diminished drop in pressure, the drop was

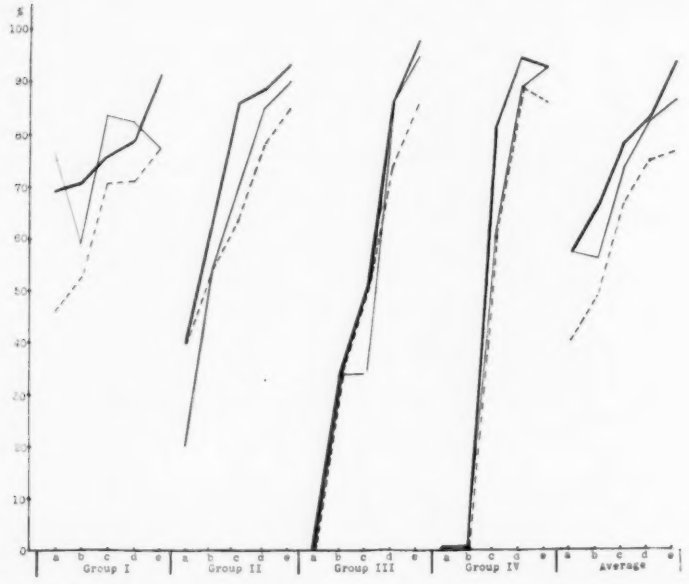

Fig. 2.—The percentage incidence of response at various ages in the four blood pressure groups designated in table 1 and the average for the four groups. The heavy solid lines represent the total number of patients that responded; the thin solid lines, the number giving a systolic response, and the broken lines, the number giving a diastolic response. In each blood pressure group ages are signified as follows: *a*, 20 years or less; *b*, 21 to 30 years; *c*, 31 to 40 years; *d*, 41 to 50 years, and *e*, over 50 years.

actually greater in hypertension. This observation corroborates the findings of Koch,[10] Lian, Stoicesco and Vidrasco,[20] Mandelstamm and

20. Lian, C.; Stoicesco, S., and Vidrasco, G.: De l'état du système nerveux végétatif dans l'hypotension et l'hypertension artérielle permanente, Presse méd. **37**:1309, 1929.

TABLE 2.—*Incidence and Degree of Response to Stimulation of the Carotid Sinus at Various Ages in Four Blood Pressure Groups* *

Blood Pressure Group	Age of Patients, Yr.	Total Number of Patients	A. Incidence of Drop in Blood Pressure: Patients Responding		Systolic Response		Diastolic Response		B. Degree of Drop in Blood Pressure: Less Than 10 Mm.				10-25 Mm.				25-50 Mm.				Over 50 Mm.			
									Systolic		Diastolic		Systolic		Diastolic		Systolic		Diastolic		Systolic		Diastolic	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
I	Under 20	13	9	69.2	10	76.9	6	46.1	2	15.3	4	30.6	4	30.6	2	15.3	3	23.1	0	0.0	1	7.4	0	0.0
	21-30	37	26	70.2	22	59.4	18	52.9	4	10.8	7	18.9	14	37.8	7	18.9	4	10.8	3	8.1	0	0.0	1	2.7
	31-40	64	49	75.5	47	83.9	45	70.3	5	7.8	13	20.3	25	39.0	19	29.5	16	25.0	13	20.3	1	1.5	0	0.0
	41-50	79	62	78.4	63	82.9	56	70.9	7	8.9	18	22.7	27	34.1	22	27.8	27	34.1	16	20.2	2	2.5	0	0.0
	Over 50	136	124	91.1	105	77.7	104	77.0	12	8.9	20	14.7	22	16.1	52	38.2	55	40.4	32	23.6	16	11.0	1	0.73
	Total	329	270	79.9	247	75.0	229	66.5	30	9.1	62	18.8	92	27.9	102	31.0	105	31.9	64	19.7	20	6.1	2	0.6
II	Under 20	5	2	40.0	1	20.0	2	40.0	0	0.0	1	20.0	0	0.0	0	0.0	1	20.0	1	20.0	0	0.0	0	0.0
	21-30	13	8	61.5	7	53.8	7	53.8	1	7.4	5	38.4	6	46.1	1	7.4	0	0.0	1	7.4	0	0.0	0	0.0
	31-40	30	26	86.6	25	83.8	19	63.3	0	0.0	5	16.6	15	50.0	8	26.6	9	30.0	5	16.6	1	3.3	1	3.3
	41-50	44	39	88.7	37	84.1	34	77.2	6	13.6	7	15.9	8	18.1	15	34.0	17	38.4	11	25.0	6	13.6	1	2.2
	Over 50	115	108	93.0	103	89.5	97	84.3	5	4.3	16	13.9	23	20.0	49	42.6	51	44.3	29	25.2	24	20.8	3	2.6
	Total	207	183	88.4	173	83.5	159	76.8	12	5.7	34	16.4	52	25.1	73	35.2	78	37.1	47	22.7	31	14.9	5	2.4
III	Under 20	1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	21-30	3	1	33.3	1	33.3	1	33.3	0	0.0	1	33.3	0	0.0	0	0.0	1	33.3	0	0.0	0	0.0	0	0.0
	31-40	6	3	50.0	2	33.3	3	50.0	0	0.0	0	0.0	0	0.0	3	50.0	1	16.6	0	0.0	1	16.6	0	0.0
	41-50	15	13	86.6	13	86.6	11	73.3	1	6.6	0	0.0	5	33.3	7	46.6	3	20.0	4	26.6	4	26.6	0	0.0
	Over 50	75	73	97.3	71	94.6	64	85.3	4	5.3	5	6.6	13	17.3	14	18.6	20	26.6	37	49.3	36	48.0	8	10.6
	Total	100	90	90.0	87	87.0	79	79.0	5	5.0	6	6.0	18	18.0	24	24.0	25	25.0	41	41.0	41	41.0	8	8.0
IV	Under 20	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	21-30	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	31-40	5	4	80.0	3	60.0	3	60.0	0	0.0	0	0.0	0	0.0	0	0.0	2	40.0	2	40.0	1	20.0	1	20.0
	41-50	18	17	94.0	16	88.8	16	88.8	0	0.0	3	16.6	2	11.1	1	5.5	5	27.7	10	55.5	9	50.0	3	16.6
	Over 50	41	38	92.6	38	92.6	33	80.4	1	2.4	1	2.4	5	12.2	9	21.9	14	34.1	16	39.0	18	43.9	7	17.1
	Total	64	59	92.1	57	89.1	52	82.5	1	1.5	4	6.2	7	10.5	10	15.6	21	32.8	28	43.7	28	43.7	11	18.7

* The blood pressure groups are the same as those designated in table 1.

Lifschitz [12] and others. In fact, my findings indicate that the higher the original blood pressure the greater the incidence of drop. A drop occurred more often in the systolic pressure than in the diastolic in all blood pressure groups in both males and females.

The incidence of response in this series was somewhat greater than in the series of 128 cases studied by Weiss and Baker [11] and the 335 cases studied by Mandelstamm and Lifschitz.[12] In the latter series

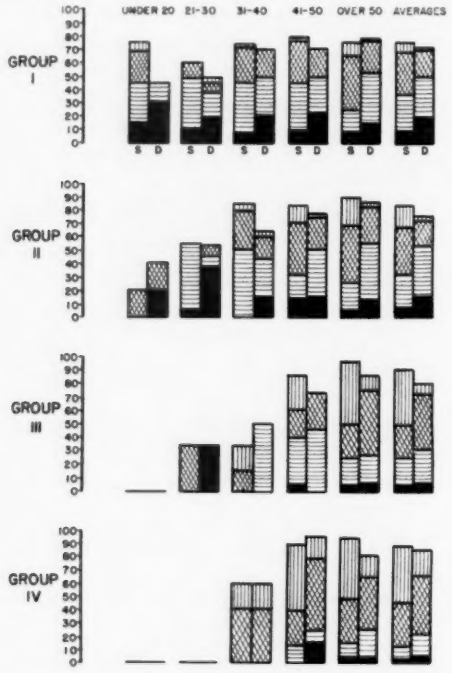

Fig. 3.—The degree of response in the various blood pressure groups at given ages, as illustrated in figure 2. Under each age group *S* stands for a systolic and *D* for a diastolic response. Representing the percentage of patients responding, the black sections signify a drop in pressure of less than 10 mm.; those with horizontal lines, a drop of 10 to 25 mm.; those with crosshatching, a drop of 25 to 50 mm., and those with vertical lines, a drop of over 50 mm.

the smaller incidence was probably due to the fact that the authors did not include among the responsive subjects those with a drop in pressure of less than 10 mm.

The degree of response, measured in millimeters of drop in pressure, also varies with the blood pressure group and with sex. Usually, the

TABLE 3.—*Average Incidence and Degree of Response to Stimulation of the Carotid Sinus at Various Ages for the Entire Series of Seven Hundred Patients*

Age of Patients, Yr.	Total Number of Patients	A. Incidence of Drop in Blood Pressure						B. Degree of Drop in Blood Pressure											
		Patients Responding		Systolic Response		Diastolic Response		Less Than 10 Mm.				10-25 Mm.				25-50 Mm.			
								Systolic		Diastolic		Systolic		Diastolic		Systolic		Diastolic	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Under 20	19	11	57.9	11	57.9	8	42.1	2	10.5	5	26.3	4	21.1	2	10.5	4	21.1	1	5.2
21-30	53	35	66.0	30	56.5	26	49.0	5	9.4	13	24.3	20	37.7	8	15.1	5	9.4	4	7.5
31-40	105	82	78.1	77	73.3	70	66.6	5	4.7	18	17.1	40	38.1	30	28.4	28	26.6	20	18.9
41-50	156	131	83.9	129	82.6	117	75.0	14	8.9	28	11.6	42	26.2	45	28.2	52	33.3	41	25.6
Over 50	367	343	93.4	317	86.3	280	76.3	22	6.4	42	11.1	63	17.1	124	33.7	140	38.1	114	31.1

Age of Patients, Yr.	B. Degree of Drop in Blood Pressure			
	Over 50 Mm.			
	Systolic		Diastolic	
	No.	%	No.	%
Under 20	1	5.2	0	0.0
21-30	0	0.0	1	1.8
31-40	4	3.8	2	1.9
41-50	21	13.4	4	2.5
Over 50	94	25.3	19	5.1

higher the original blood pressure the greater the drop. Thus, in the group with normal blood pressure and in the group with low grade hypertension a relatively greater number of patients showed a drop of less than 10 mm. than in the groups with higher grades of hypertension. In the last-mentioned groups a relatively greater number showed the higher degrees of drop in pressure. Comparatively few subjects in the normal group and in the group with low grade hypertension showed a drop of over 50 mm. In the group with the higher grades of hypertension, on the other hand, the percentage showing such a drop was great. In general, females showed a lesser degree of drop than did males in all groups.

The Age Incidence and Degree of Response.—In the course of this study it was found that there is a definite increase in frequency and in

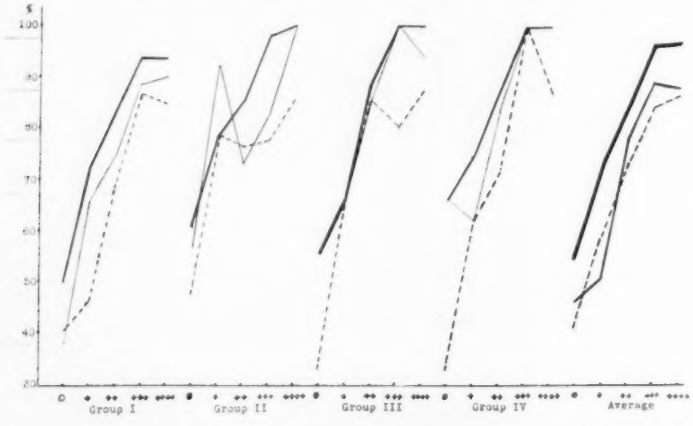

Fig. 4.—The percentage incidence of drop in blood pressure in relation to cardio-inhibition in each blood pressure group and the average for all groups. The heavy solid lines represent the number of patients that responded; the thin solid lines, the number giving a systolic response, and the broken lines, the number giving a diastolic response. The pulse marks have the same significance as those employed in table 4. The blood pressure groups are the same as those designated in table 1.

degree of response as age advances. I found no reference to this fact in the literature.

Tables 2 *A* and 3 *A* and figure 2 show the incidence of response among the 700 patients according to age and blood pressure grouping and the average for all patients.

It will be seen that in each blood pressure group the percentage of patients responding was lower at the younger ages and increased as age advanced. This observation applies both to the patients who showed

TABLE 4.—*Incidence and Degree of Drop in Blood Pressure in Relation to Degree of Cardioinhibition in Four Blood Pressure Groups* *

Blood Pressure Group	Vagal Response †	Total Number of Patients	A. Incidence of Drop in Blood Pressure: Patients Responding No.	%	Systolic Response No.	%	Diastolic Response No.	%	B. Degree of Drop in Blood Pressure: Less Than 10 Mm. Systolic No.	%	Diastolic No.	%	10-25 Mm. Systolic No.	%	Diastolic No.	%	25-50 Mm. Systolic No.	%	Diastolic No.	%	Over 50 Mm. Systolic No.	%	Diastolic No.	%
I	0	42	22	50.0	16	38.0	17	40.4	3	7.1	7	16.6	10	23.8	9	21.4	3	7.1	1	2.3	0	0.0	0	0.0
	+	49	35	71.6	31	65.3	23	46.9	8	16.5	12	24.4	13	26.5	9	18.3	9	18.3	2	40.8	1	20.4	0	0.0
	++	87	71	82.7	65	74.7	60	68.9	9	10.3	18	20.6	29	33.1	30	34.4	22	25.1	12	13.8	2	2.3	1	1.1
	+++	61	57	93.4	54	88.5	53	86.8	5	8.1	12	19.6	20	32.7	20	32.7	23	37.7	18	28.2	6	9.8	1	1.6
	++++	90	85	93.3	81	90.0	76	84.4	5	5.5	13	13.3	20	22.2	34	36.6	48	53.3	31	36.6	11	12.2	0	0.0
II	0	23	14	60.9	13	56.5	11	47.8	4	17.4	5	21.7	8	34.8	5	21.7	1	4.3	1	4.3	0	0.0	0	0.0
	+	28	22	78.5	26	92.8	22	78.5	0	0.0	9	32.2	11	39.2	11	39.2	12	42.8	2	7.1	3	10.7	0	0.0
	++	55	47	85.4	43	78.1	42	76.3	2	3.6	10	18.2	15	27.1	20	36.3	22	40.0	12	21.8	4	7.3	0	0.0
	+++	59	58	98.3	49	83.0	46	77.9	4	6.7	9	15.1	12	20.3	21	35.6	20	33.9	16	27.1	11	18.6	0	0.0
	++++	42	42	100.0	42	100.0	38	90.4	2	4.8	1	2.4	6	14.2	16	38.1	21	50.0	16	38.1	13	30.9	5	11.9
III	0	9	5	55.5	5	55.5	3	33.3	1	11.1	1	11.1	2	22.2	1	11.1	0	0.0	0	0.0	2	22.2	0	0.0
	+	9	6	66.6	6	66.6	6	66.6	1	11.1	1	11.1	0	0.0	0	0.0	0	0.0	5	55.5	5	55.5	0	0.0
	++	28	25	89.3	24	85.7	24	85.7	2	7.1	4	14.3	5	17.1	9	32.1	6	21.4	10	35.7	10	35.7	0	0.0
	+++	21	21	100.0	21	100.0	17	80.9	1	4.7	0	0.0	4	19.0	5	23.8	8	38.1	11	52.3	7	33.3	4	19.0
	++++	33	33	100.0	31	93.9	29	87.8	0	0.0	0	0.0	7	21.2	9	27.2	11	33.3	15	45.4	15	42.3	4	12.1
IV	0	3	2	66.6	2	66.6	1	33.3	0	0.0	0	0.0	0	0.0	0	0.0	1	33.3	1	33.3	1	33.3	0	0.0
	+	8	6	75.0	5	62.5	5	62.5	0	0.0	1	12.5	1	12.5	0	0.0	2	25.0	3	37.5	2	25.0	1	12.5
	++	18	16	88.8	15	83.3	13	72.2	0	0.0	1	5.5	2	11.1	7	38.8	8	44.4	3	16.6	5	27.7	2	11.1
	+++	20	20	100.0	20	100.0	20	100.0	0	0.0	1	5.0	3	15.0	1	5.0	8	40.0	14	70.0	9	45.0	4	20.0
	++++	15	15	100.0	15	100.0	13	86.6	1	6.6	1	6.6	1	6.6	2	13.3	2	13.3	6	40.0	11	73.3	4	26.6

* The blood pressure groups are the same as those designated in table 1.

† The degrees of cardioinhibition are represented by the following symbols: 0, no slowing of the heart; +, less than 10 per cent slowing; ++, 10 to 30 per cent slowing; +++, 30 to 70 per cent slowing, and ++++, stoppage of the heart for three seconds or more.

a combined systolic and diastolic drop and to those who showed a drop of either the systolic or the diastolic pressure alone. The higher the original blood pressure the greater the incidence of the drop in all age groups but particularly in the older groups.

The degree of response likewise increased with advancing age, as shown in tables 2 *B* and 3 *B* and figure 3. It varied with the extent of the original blood pressure, however. In the group with normal

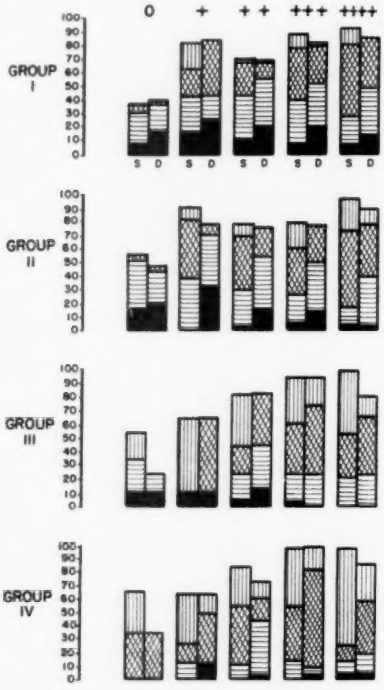

Fig. 5.—The degree of cardioinhibition in relation to the degree of fall in blood pressure. The plus marks have the same significance as those employed in table 4. The blood pressure groups are the same as those designated in table 1. The sectional subdivisions representing the degrees of drop in blood pressure are the same as those employed in figure 3; *S* signifies systolic blood pressure, and *D* signifies diastolic blood pressure.

blood pressure a relatively greater number of patients showed a low degree of drop in pressure at all ages. As the blood pressure rose, the degree of drop increased in every age group, but the increase was always greater at the older ages.

TABLE 5.—*Incidence and Degree of Drop in Blood Pressure in Relation to Degree of Cardioinhibition for the Entire Series of Seven Hundred Patients*

Vagal Response *	Total Number of Patients	A. Incidence of Drop in Blood Pressure						B. Degree of Drop in Blood Pressure													
		Patients Responding		Systolic Response		Diastolic Response		Less Than 10 Mm.				10-25 Mm.				25-50 Mm.				Over 50 Mm.			
								Systolic		Diastolic		Systolic		Diastolic		Systolic		Diastolic		Systolic		Diastolic	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0	77	43	55.8	36	46.7	32	41.5	8	10.3	13	16.8	20	25.9	15	19.4	5	6.4	3	3.8	3	3.8	0	0.0
+	94	69	73.4	68	51.0	56	59.5	9	9.5	23	24.4	25	26.4	20	21.2	23	24.4	12	12.7	11	11.6	1	1.1
++	188	159	84.0	147	78.2	139	73.9	13	6.9	33	17.5	51	27.1	66	35.1	58	30.8	37	19.6	21	11.1	3	1.5
+++	161	156	96.8	144	89.4	136	84.4	10	6.2	22	13.0	39	24.2	47	29.1	59	36.6	59	36.6	33	20.4	9	5.6
++++	180	175	97.2	169	88.3	156	86.6	8	4.4	15	8.3	34	13.3	61	33.8	84	46.6	68	37.7	48	26.6	13	7.2

* See table 4 for the designation of degrees of cardioinhibition.

The Relation of the Vasodepressor to the Cardioinhibitory Reflex.—As said before, the vasodepressor and the cardioinhibitory reflex may coexist in the same or in different degrees in the same person; both may be absent, or each may occur alone. The incidence of their coexistence and the degree of the two reflexes are shown in tables 4 *A*, 4 *B*, 5 *A* and 5 *B* and in figures 4 and 5.

It will be noted that a good proportion of patients who showed no cardioinhibition had the vasodepressor reflex. The degree of drop in pressure in such patients was on the average relatively smaller than in those who also showed cardioinhibition. Also, a fairly large proportion of patients who showed no vasodepression showed cardioinhibition. In these persons, however, the very high degree of cardioinhibition were not observed except in the group with normal blood pressure.

In general, the greatest number of patients showing cardioinhibition also showed vasodepression, and the degrees of the two reflexes on the whole corresponded.

COMMENT

It is not my intention in this paper to prove or disprove Hering's theory that hypertension may be caused by absence of the vasodepressor reflex of the aortic nerves and the carotid sinuses. Mannaberg's [21] contention that he found no slowing of the heart in his series of 241 hypertensive patients, which is offered as proof that the carotid sinus sensory receptors are insensitive to endarterial pressure, cannot be definitely substantiated. In my series the average heart rate was about the same in the normal as in the hypertensive subjects. Also, the finding by Hering and others that diminution in the endosinal pressure due to compression of the common carotid arteries failed to raise the blood pressure in hypertensive patients, as it would be expected to do if the carotid sinus nerve terminals had normal function, could not be substantiated in Gammon's [17] cases and in some of the cases in which I tried it.

Regardless of whether or not insensitivity of the sinus regions and the aortic depressor nerves is the cause or one of the causes of essential hypertension, and especially if it is the cause, the mechanism of a hyperactive vasodepressor carotid sinus reflex has not as yet been explained. Why a hyperactive reflex occurs with great frequency and in a higher degree in hypertension and why its frequency and degree increase with an increase in blood pressure still call for an explanation, as do its increase with advancing age and its more frequent occurrence in males.

That the hyperactive reflex is caused by an increase in local sensitivity of the nerve terminals because of degenerative changes in the carotid

21. Mannaberg, J., cited by Heymans, Bouckaert and Regniers.[8]

arteries is not conceivable. Also, that compression of the nerve terminals against a rigid calcified sclerotic intima, as suggested by Sunder-Plassmann,[22] may be the cause is possible only in a few cases, in which there is local calcification of the carotid artery. In the great majority of cases there are not enough local arterial changes which would provide greater resistance to compression of the nerve terminals than that offered by the spinal column, against which the carotid sinus is compressed in performance of the test. Furthermore, many patients with pronounced local sclerosis show no hyperactivity. The lack of a relationship between a hyperactive reflex and local sclerosis of the carotid arteries was best demonstrated in the autopsy material reported on by Keele.[23] Finally, the fact that the response is usually greater with the patient in the upright position than with him in the recumbent posture speaks against fixed local pathologic change in the carotid arteries as the cause for hypersensitivity.

In the light of these findings, it must be assumed that a hyperactive vasodepressor carotid sinus reflex is due to changes in the synapses between the afferent and the efferent portions of the arc in the medulla or to localized changes in the vasomotor terminals of the vessels which make them lose their tonic effect reflexly.

The unequal effect of the carotid sinus reflex on the blood pressure and pulse rate and in the production of other manifestations in the same person is most likely due to differences in the threshold of the central synapses and possibly also to differences in sensitivity of the various motor arms, as suggested by Weiss, Capps and Ferris.[24] The probability that variation in the number and in the sensitivity of the various nerve fibers leading from the carotid sinus to different regions in the medulla is to be considered. If, however, a response is due to sensitivity in the center rather than in the carotid sinus region, such an alternative cannot be definitely considered. The experimental work of Hatcher and Weiss[25] is of interest in pointing to this conception. They found that a drug applied to the same area of the medulla may produce various motor effects depending on the state of the body. Different drugs applied to the same medullary region under the same bodily conditions resulted in different responses, owing probably to a specific structural affinity of the drug for given synapses. They concluded that

22. Sunder-Plassmann, cited by Heymans, Bouckaert and Regniers.[8]

23. Keele, C. A.: Pathological Changes in Carotid Sinus and Their Relation to Hypertension, Quart. J. Med. **2**:213, 1933.

24. Weiss, S.; Capps, R. B., and Ferris, E. B.: Syncope and Convulsions Due to a Hyperactive Carotid Sinus Reflex, Arch. Int. Med. **58**:407 (Sept.) 1936.

25. Hatcher, R. A., and Weiss, S.: Studies on Vomiting, J. Pharmacol. & Exper. Therap. **22**:139, 1923.

there is considerable variation in the function of the brain centers not only in different persons but in the same person during different bodily states.

If these hypotheses are true it may be concluded that a hyperactive vasodepressor carotid sinus reflex indicates an instability in the synapses of the medullary center or in the efferent arm of the arc, which under certain provocation results in loss of the vasodepressor effect. Persons who have this unstable state may react in the same way to reflex stimulation from any region of the body, as indicated by Ferris, Capps and Weiss.[26] My report in this paper suggests that the instability becomes more marked as age advances and in the pathologic state of hypertension and is more prominent in males. The possibility is that local circulatory disturbances in the medulla or in the efferent endings of the vasomotor system in the vascular tree caused by arteriosclerosis may be the underlying factor, as this instability occurs under circumstances in which arteriosclerosis is apt to be present. In some persons it may be an inherent constitutional defect.

SUMMARY AND CONCLUSIONS

This paper covers a study of the vasodepressor effect induced by the carotid sinus reflex. Seven hundred patients were tested, most of whom had demonstrable cardiovascular disease. Of these, 447 were males and 253 females.

The patients were divided into four groups according to the original blood pressure. In group I were included subjects with normal blood pressure; in group II, patients with low grade hypertension; in group III, those with moderate hypertension, and in group IV those with marked hypertension.

It was found that, roughly, about 88 per cent of the males and 82 per cent of the females showed a drop in pressure. If a drop of less than 10 mm. is excluded as of insufficient significance, the response is reduced to about 78 per cent for males and 71 per cent for females. The response occurred more frequently and in greater degree in the older age groups. Also, the higher the blood pressure the more frequent the response and the greater its degree. A drop was more frequent in the systolic pressure than in the diastolic. A drop in pressure often occurred in patients without cardioinhibition but was more frequent in those who also showed cardioinhibition. In such patients the frequency and the degree of vasodepression roughly corresponded to those of cardioinhibition.

26. Ferris, E. B., Jr.; Capps, R. B., and Weiss, S.: Relation of the Carotid Sinus to the Automatic Nervous System and the Neuroses, Arch. Neurol. & Psychiat. **37**:365 (Feb.) 1937.

There was a marked difference in response to stimulation on the two sides in many cases. The amount of stimulation required to produce the maximum response varied from case to case and with the position of the patient.

The findings point to the existence of an inherent instability in the vasomotor system in persons who show a marked vasodepression induced by the carotid sinus reflex, which the test helps to demonstrate. The seat of this instability is either in the medullary synapses or in the vasomotor terminals in the vascular tree. Arteriosclerosis is possibly one of the underlying predisposing causes of such instability, as evidenced by the fact that the reflex is most prevalent under circumstances in which arteriosclerosis is apt to occur, that is, when the patient is a man, is of advanced age and has a high degree of hypertension.

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ROENTGEN RAY TREATMENT OF HYPERTHYROIDISM

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Hyperthyroidism holds a unique position among the diseases properly falling into the field of internal medicine because, although its causation is unknown, an empiric treatment has been evolved that is satisfactory in the majority of cases. Except in certain situations, the factors that cause the thyroid to hyperfunction are obscure. Yet in most cases subtotal ablation of the thyroid relieves most of the symptoms.

In the early years of the twentieth century, the roentgen ray frequently was employed as a means of destroying the thyroid, and evidences of its success are abundant.[1] Its use became extensive at that time because of the high surgical mortality. However, since 1923 the preoperative preparation of patients with administration of iodine and other measures has brought about a decline in surgical mortality.[2] Consequently, at the present time in the major clinics of this country the mortality rate is from

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Read at the Twenty-Seventh Annual Meeting of the Radiological Society of North America on Dec. 5, 1941.

From the Divisions of Medicine and Radiology and the Thyroid Committee of the University of California Medical School and Hospital.

The members of the Thyroid Committee are Dr. Henry H. Searls, Dr. Carl L. Hoag, Dr. H. G. Bell and Dr. Leon Goldman, of the Department of Surgery; Dr. Karl B. Eichorn, of the Department of Pathology; Dr. Robert S. Stone, of the Department of Radiology; Dr. W. J. Kerr, Dr. Evelyn Anderson and Dr. Mayo H. Soley, of the Department of Medicine, and Dr. W. A. Reilly, of the Department of Pediatrics.

1. Means, J. H., and Holmes, G. W.: Further Observations on the Roentgen-Ray Treatment of Toxic Goiter, Arch. Int. Med. **31**:303 (March) 1923. Pfahler, G. E.: Roentgen-Ray Treatment of Hyperthyroidism, Radiology **34**:43-52, 1940 (with comprehensive bibliography). Smith, A. D., and Stenstrom, K. W.: X-Ray Therapy in Diffuse Hyperplasia of the Thyroid, Tr. Third Internat. Goiter Conf. & Am. A. Study of Goiter, 1938, pp. 527-532.

2. Thompson, W. O.; Taylor, S. G., III, and Meyer, K. A.: Factors Influencing Operative Mortality in Exophthalmic Goiter, Ann. Int. Med. **8**:350-359, 1934. Thompson, W. O.; Taylor, S. G., III; Meyer, K. A., and McNealy, R. W.: Experiences in Treating Toxic Goiter in a Large Public Hospital, Ann. Int. Med. **12**:217-231, 1938.

0.5 to 2 per cent during the immediate postoperative period, although in many hospitals it still is several times the latter figure. Because of the reduction in surgical mortality, many of the foremost students in this country believe that subtotal thyroidectomy is the treatment of choice for hyperthyroidism and give little credit to roentgen ray therapy.

Fig. 1.—Low power section of thyroid tissue from a patient cured of exophthalmic goiter by roentgen irradiation (patient died four years after treatment of a tumor of the brain).

Roentgen rays have a profound effect not only on the smaller arterial vessels that supply the thyroid but on the acini and the supporting structures of the gland. Figures 1 and 2 show sections of thyroid tissue from a patient who had had hyperthyroidism with a metabolic rate in the low plus thirty's. After adequate roentgen ray therapy his metabolism had fallen to about — 30 per cent and his clinical symptoms had been relieved.

Four years later he died from a tumor of the brain. The thyroid tissue obtained at autopsy was firm and hard and weighed only a few grams. On microscopic examination it showed extensive fibrosis, destruction of the acini and intimal, subintimal and medial thickening of the smaller arteries. Probably the thyroids of most of the patients "cured" by roentgen ray treatment would present a similar appearance both grossly

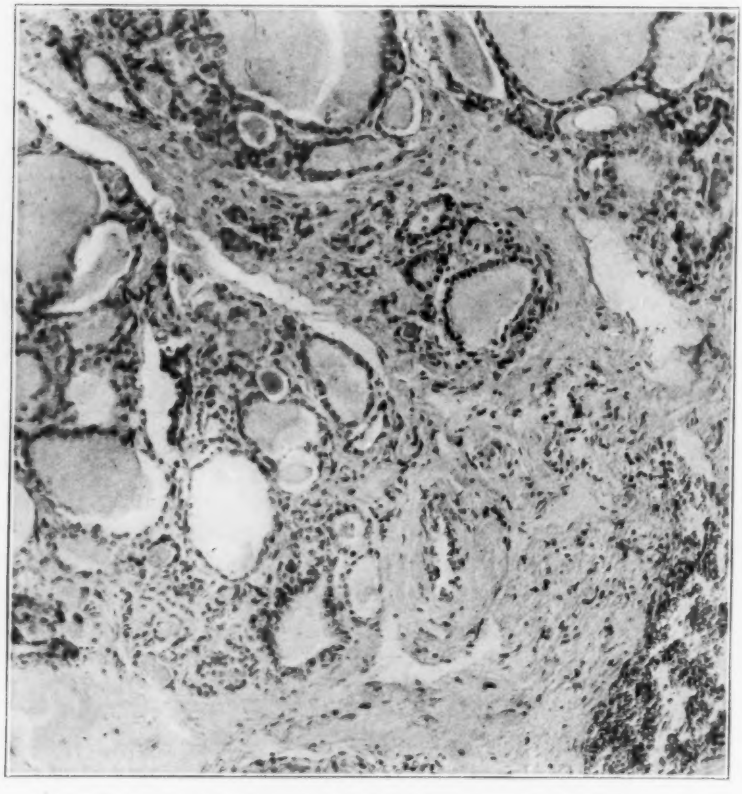

Fig. 2.—Higher magnification of tissue shown in figure 1.

and histologically. Figures 3 and 4 show sections of thyroid tissue from a young girl with extremely severe hyperthyroidism. She had been treated intensively with roentgen rays up to six weeks prior to subtotal thyroidectomy as preparation for the surgical procedure. The tissue from this patient shows an earlier stage of destruction than that from the previous patient, but again there are pronounced fibrosis, destruction of much of the acinar tissue and thickening of the smaller vessels. The

sections from these 2 patients give evidence of the ability of roentgen rays to destroy hyperplastic thyroid tissue and demonstrate the changes that might be expected as a result of successful roentgen ray therapy.

The following study was undertaken because of the neglect of roentgen ray therapy in recent years. Certain definite purposes were kept in mind: first, to determine as far as could be done by clinical examination

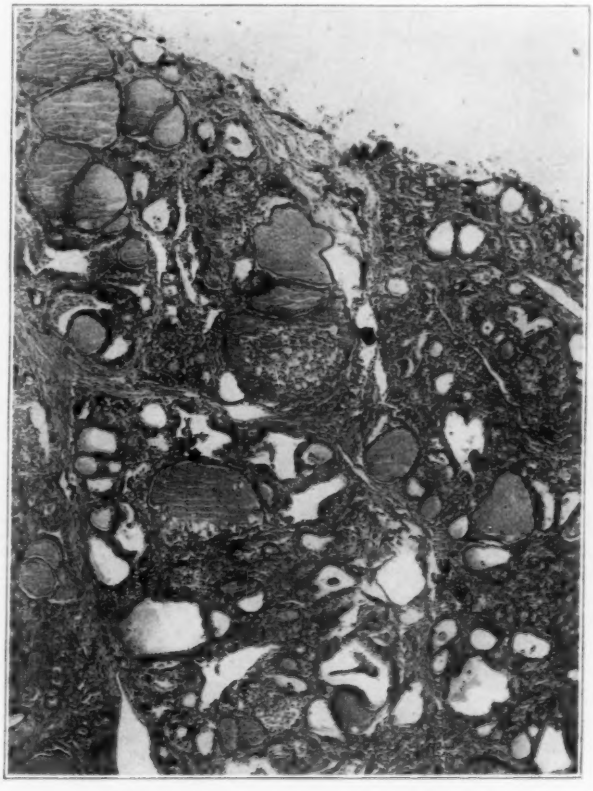

Fig. 3.—Section of thyroid tissue from a patient who received extensive irradiation to the thyroid (two courses) up to six weeks before subtotal thyroidectomy. This patient received irradiation preparatory to surgical treatment.

and laboratory tests whether or not subtotal destruction of the thyroid could be achieved and if it could be what dosage was necessary; secondly, to outline criteria for the selection of patients for whom roentgen ray therapy might be the treatment of choice, and, thirdly, to present a series

of patients who were followed carefully by one observer over a period of several years. (The method of following patients is illustrated in table 1.)

All the patients in our relatively small series of 43 [3] had unquestioned hyperthyroidism. The selection was carried out in part by the members of the Thyroid Committee of the University of California Hospital. This

Fig. 4.—Higher magnification of tissue shown in figure 3. Note the fibrosis and change in blood vessels.

committee consists of a group of internists, surgeons, roentgenologists and pathologists particularly interested in diseases of the thyroid. It has

3. These comprised only the group seen in the clinic. A total of over 200 patients, both clinic and private, were seen by the members of the Thyroid Committee during the last twelve years; however, they were not followed in a manner that would allow an adequate and objective appraisal of the ability of roentgen rays to achieve a subtotal destruction of hyperplastic thyroids.

Name: Lena Dunnell. O.P. D. No.: U4395. Age: 37 years. Diagnosis: Toxic nodular goiter.

Date	Therapy	Weight	Basal Metabolic Rate	Pulse	Rhythm	Blood Pressure	Goiter	Eye Signs	Nervousness	Tremor	Dyspnea	Palpitation	Tachycardia	Weakness	Heat Intolerance	Headache	Gastrointestinal Data	Catamenia	Comment
3/20/36	.....	.....	+58%																
3/30/36	No iodine except iodized salt	137.3	+39%	120	Reg.	160/80	+ (nodular)	+	++	+	+	++	++	++	+ (always)	Occ.	++	Reg. and scanty	
4/21/36 to 4/27/36	Roentgen therapy																		
4/27/36	Phenobarbital 0/015, 4 t. d.	142½	.....	114	S. A.	146/74	+	+	++	+	+	++	+	++	+ (always)	Occ.	—	Flow greater	
6/ 1/36	Phenobarbital 0/015, 4 t. d.	145½	.....	102	S. A.	156/80	+	Stare only	+	Sl.	Sl.	++	+	—	+ (always)	Occ.	—	Scanty	
6/20/36	None since 6/1/36	147½	.....	72-75	S. A.	124/80	+	Stare only	—	—	—	+	±	—	Less	Less	—	Less scanty	
6/15-6/20	Roentgen therapy																		
8/ 6/36	None	149	—18%	72	Reg.	138/86	+	Stare only	—	—	—	—	—	—	—	Occ.	Reg.	Less scanty	
1/26/37	None	148½	+ 9%	81	Reg.	134/80	Less	—	—	—	—	—	—	—	—	Occ.	Const.	Sl. scanty	
3/ 1/37	None	152	.....	78	Reg.	140/80	Palpable only Nodular	—	—	—	—	—	—	—	—	Occ.	Const.	Sl. scanty	
5/10/37	None	154	0	78	Reg.	160/88	Palpable only Nodular	—	+	—	—	Occ.	—	—	—	Occ.	Const.	Sl. scanty	
4/25/38	None	152½	+15%	84	Reg.	162/100	Palpable only Nodular	—	+	—	—	+	—	—	—	—	—	Sl. scanty	
5/ 4/38	Phenobarbital 0/032 t. i. d. since 4/25/38	155½	+13%	72	Reg.	170/90	Same	—	Less	—	—	+	—	—	—	—	—	1 day shorter	
5/9/38 to 5/14/38	Roentgen therapy																		
9/23/38	None for 3 months	163½	.....	72	Reg.	132/84	Same	—	—	—	—	—	—	—	—	—	—	Reg. and normal	
12/13/38	None (diet reduced)	165	— 9%	72	Reg.	166/90	Normal size; nodular	—	—	—	—	—	—	—	—	—	—	Reg. and normal	
6/20/39	None	158½	.....	72	Reg.	134/82	Normal size; nodular	—	—	—	—	—	—	—	—	—	—	Reg. and normal	Hot flashes
1/19/40	None	167½	—16%	72	Reg.	148/90	Barely palpable; nodular	—	+	—	—	+	+	—	—	—	—	Reg. and normal	Spells of nervousness, palp. and tach., nausea
9/13/40	None	167	.....	78	Reg.	134/90	Barely palpable; nodular	—	+	—	—	+	—	—	—	—	—	Reg. and normal	Spells of nervousness, palp. and tach., nausea
3/11/41	None	165	.....	..	.....	.....	Barely palpable; nodular	—	Occ.	—	—	Occ.	Occ.	—	—	—	—	Reg. and normal	Spells of nervousness, palp. and tach., nausea, plus stabbing pains in chest
(Patient in menopause and very worried about son who has been drafted into army)																			
8/15/41	None (Still upset about son)	162	.....	78	S. A.	170/100	Barely palpable; nodular	—	Occ.	—	—	Occ.	Occ.	—	—	—	—	Reg. and normal	

been in existence since 1929 and meets once a week to discuss problem cases and to guide the therapy of all clinic patients at the University of California Hospital. In the choice of patients for roentgen ray therapy, the following criteria were applied: 1. Only patients who were moderately ill with hyperthyroidism were chosen; patients about whom there was doubt were excluded, and very toxic patients were excluded whenever possible. 2. Patients without complications, such as rheumatic heart disease with mitral stenosis, were preferred. 3. As soon as it had been proved that patients with nodular goiter could be "cured" by treatment with roentgen rays, other such patients were omitted from this series. Thereafter only those patients were included who had had undoubted exophthalmic goiter and had a postoperative recurrence as a result of which the thyroid felt nodular on palpation but who, according to our experience with similar patients, probably did not have true or encapsulated adenoma. 4. The breadwinner of a family was not chosen for roentgen ray therapy unless the disease was of such a degree of severity that he could continue to work while undergoing treatment. 5. Patients with pulmonary tuberculosis or other diseases of the apexes of the lungs were preferably excluded. 6. For obvious reasons patients who lived at great distances were omitted from this series. Points 4 and 6 would not necessarily apply to private patients or to patients not included in a study of this kind.

TECHNIC

The technic of the roentgen treatment of hyperthyroidism has undergone many changes over a period of years. Since the present series of treatments was begun, only one change, namely a change in voltage, has been made. In the majority of cases the treatments were given with roentgen rays produced by a current with 100 kilovolts and 10 milliamperes of constant potential. The radiations were filtered through 0.25 mm. of copper and 1 mm. of aluminum, a beam with a half value layer of 6.8 mm. of aluminum being produced. The target-skin distance used was 40 cm., and the number of roentgens was approximately 20 per minute (measured in air). Treatments were directed to each lobe of the thyroid separately, and the fields were made large enough so that they extended beyond the limits of the lobe. They frequently were 10 by 7 or 10 by 8 cm. in size. The lower border of the thyroid fields was made to coincide with the upper edge of the sternum. A narrow strip of skin was left between the two oblique fields. The thymus field extended in the midline from the top of the sternum down 10 cm. The radiations were directed obliquely inward from each lateral field. In adjusting the angle an attempt was made not to cross fire but to direct the beam as nearly perpendicularly to the skin as possible. When the angles were such that there was cross fire at the level of the back of the trachea or the esophagus, the patient had considerable reaction, with irritation of either or both these structures.

In routine treatment the patients received 150 roentgens, as measured in air, to each lobe of the thyroid every day for six days; thus, a total of 900 roentgens (in air) was administered to each lobe. During the same period the patients

received 150 roentgens (in air) every second day to the thymus region, so that during the six day period a total of 450 roentgens was administered to the thymus. Such a series of irradiations completed what we term one course of treatment. During the following two or three weeks the patients frequently showed faint erythema or slight but persistent pigmentation. As stated, whenever a cross fire effect on the esophagus or on the trachea was created from fields that were too oblique, some irritation of the mucosa of these structures followed, which caused difficulty in swallowing or an irritative cough.

This technic was used for all patients in the series except those who received treatments on the 200 kilovolt apparatus. This apparatus consisted of a constant potential machine; the rays were filtered through 0.7 mm. of copper and 1 mm. of aluminum at a distance of 50 cm. The half value layer of this radiation was 1.05 mm. of copper. In one series to one patient and in three series to another patient, a course of treatments was given over one anterior field 10 by 10 cm. in size to the thyroid and over a field of the same size to the thymus. Since this type of irradiation is given at a greater target-skin distance and affords no chance of cross fire on the esophagus, we believe equally good results are obtained without the risk of certain adverse effects. Although the stated dose, 150 roentgens in air, is not the same on the skin when it is delivered by the different qualities of radiation (100 kilovolts and 200 kilovolts) because of difference in back scatter, the dose delivered to the tissue of the thyroid gland is so nearly the same that we consider the two methods equally satisfactory.

After a one week course of radiation, the patient was kept under medical observation for six weeks, during the last week of which time he was reexamined. Unless he showed remarkable improvement (as did 1 patient), he was given a second course of treatments, which was administered in the same manner. Again, a period of observation of about twelve weeks followed, during the last week of which the patient's condition was thoroughly reevaluated and a decision was reached as to whether or not a third course should be given. We believe definitely that treatment should not be discontinued until the clinical findings, including the basal metabolic rate, are normal or below normal. The cause for most of the recurrences which follow roentgen ray treatment is the failure to accomplish subtotal destruction of the thyroid.

Before the present method was adopted, treatments were given once a week and to only one lobe of the thyroid at a time. Later treatment was given once a week to both lobes of the thyroid and to the thymus. By the present technic, the necessary amount of radiation is administered in a comparatively short period of time with only a slight cutaneous reaction, and a period of comparative freedom from symptoms intervenes before further therapy becomes necessary.

RESULTS

The present study was begun in 1935. From that time until September 1940, 43 patients with unquestioned hyperthyroidism were treated with roentgen rays in the clinic service of the University of California Hospital. Of these, 31 patients had toxic diffuse goiter and 12 had toxic nodular goiter. Of the 12 patients with nodular goiter, 7 gave a history of previous operation for exophthalmic goiter and had recurrences of nodular goiter clinically, 2 had long-standing hyperthyroidism and what might be called nodular involution and 3 had toxic

nodular goiter not previously treated. Thirty patients of the series had not been treated surgically, and 13 had recurrences after operation. The basal metabolic rate was determined prior to treatment for all patients except 1 who had pneumonia. The average metabolic rate was + 35.7 per cent before treatment and — 2 per cent after treatment. The average fall in basal metabolic rate was 35.7 per cent for the 37 patients who were either "cured" or showed marked improvement. Table 2 gives the pertinent data.

TABLE 2.—*Data on Forty-Three Patients with Hyperthyroidism*

Total number of patients		43
Women (average age 40.0 years)		37
Men (average age 46.7 years)		6
Classification		
Toxic diffuse goiter		31
Toxic nodular goiter		12
Recurrence of nodular goiter	7	
Nodular involution	2	
Toxic nodular goiter	3	
Number of patients not previously operated on		30
Number of patients previously operated on		13
Number of patients who received iodine		22
Number of patients who did not receive iodine		21

TABLE 3.—*Results of Roentgen Ray Treatment in Patients with Hyperthyroidism*

Total number of patients	43
Number of patients clinically free of hyperthyroidism	25 (58.1%)
Number of patients markedly improved	8 (18.6%)
Number of patients inadequately followed	3 (6.9%)
Average basal metabolic rate before treatment (N,* 42)	+35.7%
Average basal metabolic rate after treatment (N.* 35)	— 2.0%
Averge fall in basal metabolic rate after treatment (N,* 37)	35.7%
Avearge time between first course of roentgen ray treatment and return to normal status	8.7 months
Average gain in weight of "cured" and improved patients (N.* 39) (34 gained; 4 lost; 1 remained same)	11.1 lb. (5 Kg.)
Average decrease in pulse rate per minute (N,* 38) (34, decrease; 4, increase)	20.5 beats

* N indicates number of patients.

Twenty-five patients (or 58.1 per cent of the series) may be called "cured." By "cured" we mean that they were clinically free of signs or symptoms of hyperthyroidism (with the exception, of course, of residual exophthalmos). Eight patients (or 18.6 per cent) were markedly improved and perhaps would have been called "cured" by many workers. Three of the patients were inadequately followed. Therefore we are unable to give their status (table 3).

The results of roentgen ray treatment would appear more impressive if we eliminated 1 patient who was treated in preparation for operation, 2 patients to whom we gave roentgen ray therapy in the hope of relieving their hyperthyroidism before they died of congestive heart failure and

3 patients who were inadequately followed. Of the remaining 37 patients, 25 (or 67.6 per cent) were "cured," 8 (or 21.6 per cent) were markedly improved and in 4 (or 10.8 per cent) the treatment failed. Thus, 33 patients (or 89.2 per cent) were either completely relieved of hyperthyroidism or were markedly improved.

Three and a half months after therapy was initiated, 2 of the patients died. One, a 74 year old man, had been in congestive heart failure for four years. Roentgen ray therapy had been undertaken in the hope of curing the hyperthyroidism before he died of heart disease. The second death occurred in a 60 year old woman who had had hyperthyroidism for over ten years and had been in congestive heart failure for two years. In her case, too, roentgen ray therapy was unable to cure the hyperthyroidism before the patient died of congestive heart failure.

The treatment of 7 patients was classified as a failure (table 4). As shown in the analysis, this classification is intentionally conservative.

TABLE 4.—*"Failures" of Treatment and Complications*

Number of patients in whom roentgen ray treatment failed to bring about a "cure"		7
Number of deaths (see text)		2
Number of patients operated on after roentgen ray treatment because of		
Severity and progression	1	
Recurrence	1	
Roentgen ray burn (filter left out)	1	
One course of roentgen ray therapy given preparatory to operation	1	
Family difficulties	1	
		5
Complications		
Roentgen ray burn (filter left out)	1	
Tracheitis and esophagitis	15	

The first patient was a severely sick Chinaman who had been operated on eight months before and had a recurrence so severe that his metabolic rate was + 75 per cent. In spite of administration of iodine and two courses of roentgen ray therapy, the hyperthyroidism persisted and he became so toxic that he nearly died after a second radical thyroidectomy. Later he had characteristic myxedema. The second failure occurred in a patient who after three courses of roentgen ray therapy had shown improvement, with a decrease in the size of the thyroid to well within normal limits. She had a recurrence somewhat over a year after roentgen ray therapy was completed and was operated on because she was dissatisfied with the therapy. The remaining 5 patients whose treatment failed consisted of the 2 patients who died, a patient who was given one course of roentgen ray treatment preparatory to operation, a patient who was operated on after a roentgen ray burn on her neck (a filter had been left out during therapy) and a patient who was operated on because of a family situation which warranted treatment that would get her well as quickly as possible. It should be understood that roentgen ray therapy was given to the 2 patients who died only in the hope of saving their

lives, to the third patient only as preparation for operation and to the fourth, who in retrospect was a poor choice for this form of treatment, because certain factors in the environment had not been thoroughly appreciated. The treatment of the remaining 3 patients may be classified simply as a failure.

The statement frequently is made that achievement of a normal clinical status takes much more time by roentgen ray therapy than by subtotal thyroidectomy. For the 25 patients whom we have classified as "cured" the average length of time required for the cure was eight and seven-tenths months. By "cured" we mean afforded complete subjective relief of the symptoms of hyperthyroidism and complete objective relief as indicated by the results of physical examination, return of the basal metabolic rate to a normal level (that is, low normal) and decrease in the size of the thyroid gland to normal. The interval between onset of treatment and "cure" undoubtedly was longer than the interval before return to normal status following partial thyroidectomy in a comparable series, but certainly not inordinately so.

Nineteen of the "cured" patients had not been operated on prior to roentgen ray treatment. Fourteen of these had three courses of treatment, 1 had two and a half courses, 3 had two courses and 1 had only one course (the last patient might well have had spontaneous recovery without roentgen ray therapy). Of 6 patients with recurrences following operation, 2 had three courses and 4 had two courses of roentgen ray treatment. As one would expect, the patients who had the most thyroid tissue required the most roentgen ray treatment.

Only 22 patients of the entire series received iodine. It was administered for an average of six and nine-tenths months. Twenty-one patients, including 11 of those "cured," received no iodine at all.

The patients were followed for an average of thirty-one and four-tenths months after treatment; of course those who died or who were operated on are excluded from this group. One of those who were inadequately followed was seen for only four months, the second for only nine months and the third for only seven and a half months. All the others were observed over a minimum of fourteen months and a maximum of sixty-four and a half months after treatment. During this time 2 had recurrences. One was operated on in the status of a private patient and later probably had postoperative hypothyroidism. The second was given a third course of roentgen ray therapy and for three years has remained normal (to November 1941).

In 38 patients the thyroid decreased to normal or small normal size. A similar change has not been stressed by other writers. Nevertheless, we consider decrease of the gland to normal size an important factor in clinical improvement. In fact, it seems inconsistent that relief of hyperthyroidism should follow roentgen ray therapy if the thyroid does not

become definitely smaller. In several cases, by the time the patient was clinically free of signs and symptoms of the disease, the thyroid was so small that the observer, in spite of his ability to palpate and estimate with reasonable accuracy thyroids that weigh 20 to 25 Gm., found difficulty in outlining the gland. In cases of severe hyperthyroidism, the decrease in the size of the thyroid may lag considerably behind the clinical improvement.

We have attempted to draw some conclusions as to changes in blood pressure as well as in pulse rate and weight (table 3) in the cured and in the improved groups. There are too many sources of error in the determination of blood pressure even under relatively standardized conditions to permit a statistical appraisal. Nevertheless certain trends were noted. Thirty-eight patients showed an average fall in the systolic pressure of 11 mm. of mercury (30 showed a decrease and 8 an increase) and an average increase in the diastolic pressure of 7.5 mm. of mercury (27 showed an increase and 11 a decrease). The fall in systolic and in pulse pressure probably reflects a decrease in the cardiac output, while the increase in diastolic pressure probably coincides with an increase in arteriolar tone commensurate with the fall in the basal oxygen consumption. As already intimated, our series is too heterogeneous, especially as to age, to allow any interpretation of the changes noted except that they may be regarded as reflecting a trend.

The presence or absence of complications is worth special attention. None of the patients who received roentgen ray therapy alone later had hypothyroidism or myxedema. However, 3 of those who were operated on after roentgen ray treatment had these conditions. The handling of an ambulatory patient during the interval after roentgen ray treatment and before improvement which brings his symptoms to subclinical ranges may need to include measures that cause him to gain weight and to overcome nervousness. Thus, we have used high calory, high carbohydrate, high vitamin diets, sedatives in adequate doses, vitamin supplements (especially vitamin A and thiamine hydrochloride) and in one half of our cases iodine in small doses (in the form of compound solution of iodine U. S. P. or potassium iodide). Iodine may be useful during the first few weeks after the first course of roentgen ray therapy or it may be necessary for much longer periods for the more toxic patients.

The most difficult problems in this series were presented by the complications of tracheitis and esophagitis. They occurred in 15 patients, 1 of whom had questionable postradiation laryngitis, and undoubtedly were caused by the original method of administering roentgen rays to the thyroid through two ports anteriorly, which resulted in cross firing on the trachea and the esophagus. Mild symptoms disappeared within a week or ten days, while severe ones persisted for as long as three weeks. Since this method has been abandoned and only one port has been used,

neither complication has appeared. No telangiectasis or atrophy of the skin was noted in this series, although many patients had initial reddening of the skin and several had tanning of the neck that persisted for months to years. Only one roentgen ray burn occurred, and this was due to an unfortunate accident by which a filter was omitted. None of the patients showed any clinical evidence of damage to the parathyroids.

COMMENT

According to the evidence presented here and elsewhere,[1] roentgen therapy can destroy sufficient thyroid tissue in patients with toxic goiter to produce the same results as surgical subtotal thyroidectomy. If both surgeon and roentgenologist are thoroughly competent, one of the important considerations is the selection of the patients. We have already outlined our criteria for selection of patients for roentgen ray therapy. We believe that patients with nodular goiter (unless they have recurrences after operation) should be operated on, because neoplastic nodules cannot be distinguished from involutionary nodules by palpation through the tissues of the neck. Since such a differentiation requires histologic examination, all patients with primary toxic nodular goiter should be treated surgically. There are other considerations that have not yet been discussed. Although we have no definite proof, we are under the impression that patients who sunburn easily are also more apt to contract tracheitis and esophagitis as a complication of radiation therapy. Perhaps their mucous membranes are more sensitive than those of other patients, or the tracheitis and esophagitis may be due to more important factors, such as the angles at which the roentgen ray tubes are directed.

If for any reason subtotal thyroidectomy seems desirable or necessary after one or more courses of roentgen ray therapy, the amount of thyroid tissue left in situ should be considerably greater than is customary in thyrotoxic patients who have not received roentgen ray treatment previously, because the likelihood of subsequent myxedema is greater. The effects of the roentgen rays continue for some time after the treatment is ended.

One important group of candidates for roentgen ray therapy are patients with hyperthyroidism in whom exophthalmos constitutes a prominent part of the clinical picture and in whom measurements of the eyes demonstrate severe degrees of proptosis. One of us [4] has reported elsewhere that in approximately 55 per cent of one series of surgically treated patients with toxic diffuse goiter, the eyes became significantly more prominent after operation, while an increase in exophthalmos occurred in only about 20 per cent of patients treated with roentgen rays.

4. Soley, M. H.: Exophthalmos in Patients with Various Types of Goiter, Arch. Int. Med. **70**:206 (Aug.) 1942.

It should be mentioned that in all such patients the eyes may appear less prominent when actually they protrude to a greater degree than they did prior to the treatment of the thyrotoxicosis. This deceptive appearance is a result of loss of the stare. Since the number of patients who have received roentgen ray therapy to the thyroid has increased, the changes in the exophthalmos deserve attention. The eyes of 22 of the series of 43 patients reported on here were measured with a Hertel (Zeiss) exophthalmometer before and after treatment, and those of 5 other patients were measured after therapy only. Six, or 27 per cent, of the 22 patients showed a progression of 1.5 mm. or more in one or both eyes, and 3, or 13.6 per cent, showed a decrease of similar magnitude. The remaining 13 patients showed no significant change. In view of the fact that the more rapid changes in thyroid function (and the consequent function of the anterior lobe of the pituitary) which accompany subtotal thyroidectomy for thyrotoxicosis may play an important role in the progression of exophthalmos, patients with severe protrusion of the eyes probably should receive roentgen ray therapy rather than surgical treatment of their thyroid condition.

Many roentgenologists believe that patients with hyperthyroidism who are to have radiation to the thyroid should not receive iodine prior to the period of treatment. This opinion is based on the fact that irradiation of the normal human thyroid has little effect on the function of the gland as observed clinically. Therefore the more abnormal or hyperplastic the thyroid the greater the expected effect of roentgen rays. Our experience does not permit confirmation or refutation of these ideas. Indeed, carefully controlled and extensive observations would be necessary to determine whether or not previous therapy with iodine diminishes the rate or the extent of destruction of thyroid tissue. Obviously, the sicker the patient the more likely he is to require a long time for recovery and temporary therapeutic measures besides roentgen ray therapy, such as administration of iodine. Consequently, the slower reaction may be attributed to the severity of the hyperthyroidism rather than to a diminished response to the same amount of radiation. On theoretic grounds, we prefer to give our patients iodine, if it is necessary at all, only after the first course of roentgen ray therapy.

SUMMARY

Forty-three patients with unquestioned hyperthyroidism have been treated by roentgen therapy to the thyroid. One half of these (22 patients) received iodine, while the other half (21 patients) received no iodine, in conjunction with the roentgen ray treatment. Twenty-five patients (or 58.1 per cent) were clinically free of hyperthyroidism in an average time of eight and seven-tenths months from the onset of treatment and eight (or 18.6 per cent) were markedly improved. Both

groups had a coincident decrease in the size of the thyroid to within normal limits. The average basal metabolic rate was + 35.7 per cent before treatment and — 2 per cent after treatment. Three patients were inadequately followed, and their exact status is unknown.

Two patients with congestive heart failure, which had been present for two and four years, respectively, prior to treatment, died before their hyperthyroidism could be "cured." Four patients were operated on because of failure of roentgen ray therapy and for other reasons. One patient deliberately had been given a single course as preparation for subtotal thyroidectomy.

Complications consisted of tracheitis and esophagitis in 15 patients. In order to avoid these complications, we have changed the method of therapy. Radiation to the thyroid now is given through one port anteriorly.

CONCLUSIONS

Roentgen ray therapy in adequate dosage is successful in bringing about subtotal destruction of the thyroid in patients with toxic diffuse goiter. In the majority it results in relief of clinical symptoms, fall of basal metabolic rate to a normal level and decrease of the thyroid to normal size.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY FOR 1942

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In the publication field several important events are to be recorded. A new journal has been launched; in January 1942 appeared the first number of the *Journal of Neuropathology and Experimental Neurology*. It is a quarterly, and the three numbers at hand show a high standard of work and bookmaking. The editors are to be congratulated on their production and on their courage in starting such a new project in wartime.

Another event of importance is the appearance of a book by Penfield and Erickson entitled "Epilepsy and Cerebral Localization."[1] This book contains more good information on fits, what they are and where they come from, than any book ever published. The point of view is that of a neurophysiologist using surgery as the chief tool, but the medical and psychologic aspects of the subject are well discussed. Experimental data in the form of careful case material are freely used, and the book is well illustrated and documented. Surgeons who work in this scientific way, looking on each operation as an experiment to be carefully recorded, have proved that they can advance certain parts of physiology, especially of neurophysiology, more than the physiologist whose observations are confined to laboratory animals.

A quite different, but also important, book is one by Lennox entitled "Science and Seizures."[2] This is aimed at the intelligent lay reader but is interesting reading for any physician. The social, therapeutic and hereditary aspects are particularly well handled.

After the last war Prof. Kurt Goldstein was for ten years director of a large institute for the study of brain injuries. His great experience was published in a series of papers in German. Many of these are not now available, so Goldstein, now clinical professor of neurology at Tufts Medical School, Boston, has written a book of 250 pages entitled "After Effects of Brain Injuries in War: Their Evaluation and Treat-

1. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield, Ill., Charles C. Thomas, Publisher, 1941.

2. Lennox, W. G.: Science and Seizures, New York, Harper & Brothers, 1941.

ment."[3] This will be most valuable for all military surgeons in a war where cerebral injury is so common. It is especially valuable because Goldstein's point of view is not that of a narrow specialist in neurologic localization but that of a biologist and a good general physician. For example, as a neurologist he knows that certain symptoms are direct sequelae of local cerebral lesions, a motor or a visual deficit, for example, but he emphasizes that the problem is never as simple as is generally assumed. One must realize that many important symptoms are not the direct result of damage to a part of the brain but an expression of the struggle of the changed organism to cope with the defect. This attempt of the organism to find a new adjustment gives rise to two kinds of symptoms: The first reveals the struggle; the second reflects the tendency to build up substitute performances which allow the organism to escape the struggle. He tries to come to terms with the outer world with his new nervous setup. This seems to cause changes in his "general functions," such as fatigability, attention and interest. Goldstein has carefully broken down these generalizations into specific reactions and has then made a diagnosis for and been able to treat patients suffering from most disturbing psychologic symptoms. More specifically, he describes methods of training and physical therapy for neurologic defects. Especially useful is the discussion of the reeducation of aphasic patients. This should be used more in civil practice for patients with aphasia from vascular lesions, who are too often given up as hopeless.

"The Central Autonomic Regulations in Health and Disease, with Special Reference to the Hypothalamus," by Heymen R. Miller,[4] is a most timely and useful book; as Fulton says in the introduction,

> The physiologic concept of central integration of autonomic mechanisms, and the significance of overlapping representation of somatic and autonomic levels of function, have been particularly slow to find recognition and application in clinical medicine.

In 1909 Karpus and Kreidl published their first paper on *"Gehirn und Sympathicus";* this work started the modern investigation of cerebral control over visceral functions and opened a great field in clinical medicine. Miller has taken this thirty-three years of work, epitomized what is now known of the physiologic and anatomic aspects in three chapters and discussed clinically and physiologically, each in a chapter, the regulation of body temperature, water and minerals, metabolism, circulation,

3. Goldstein, K.: After Effects of Brain Injuries in War: Their Evaluation and Treatment, New York, Grune & Stratton, Inc., 1942.

4. Miller, H. R.: The Central Autonomic Regulations in Health and Disease, with Special Reference to the Hypothalamus, New York, Grune & Stratton, Inc., 1942.

respiration, the gastrointestinal and the genitourinary tract, reproduction, sleep and emotions.

Gibbs and Gibbs[5] have published a beautiful "Atlas of Electroencephalography" showing the brain waves recorded from all sorts of common and rare cerebral disorders. Concurrent with the pictures is a good discussion that must be read to make the illustrations intelligible. Too many superficial observers have gained the idea from quick inspection that the authors have shown the typical and diagnostic electroencephalograms for all sorts of disease of the nervous system, from the varied forms of epilepsy to schizophrenia and multiple sclerosis. Many are shown, but few if any are typical; they are a great aid in diagnosis, but they are not diagnostic when taken apart from the rest of the record.

PSYCHOSOMATICS

The war has brought with it greatly increased emotional stress both among soldiers and among civilians. Medical symptoms closely related to neurotic disturbances are becoming common in military hospitals. Although the field of psychosomatics is new under that name, it is as old as the practice of medicine. If one tries to define it, many difficulties appear. Of course, the nervous system reaches and integrates all parts of the body, and "psyche" is the highest level of this nervous system. Logically and physiologically, therefore, psychosomatics has a place in every branch of medicine. Nevertheless, common sense dictates that the term psychosomatics refers to a clinical field, recently brought into the limelight by simultaneous advances in medicine and in psychiatry, a field where advance is urgently needed because of the effects on man of the war stresses. In short, it is an area of clinical activity which attends to the physiology of the emotions, where the psychiatrist can help the general physician and vice versa.[6]

The recent literature on psychosomatic problems is largely made up of (*a*) clinical descriptions and reports that show probable relations between emotions and medical symptoms and (*b*) attempts to analyze

5. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Boston, the Authors, 1941.

6. The six year review of the Josiah Macy Jr. Foundation (Josiah Macy Jr. Foundation: Review by the President of Activities for the Six Years Ended December 31st, 1936, New York, 1937) devotes much space to a discussion of psychosomatic problems. One paragraph is particularly apt in this discussion:

"Investigation of these problems can best be conducted through integrated clinical, physiological and psychological studies within the various clinical branches; for until the family physician, the pediatrician and the surgeon, as well as the various specialists, understand and deal with psychosomatic problems, no real advance can be made. When they do so, the term itself will be obsolete, for the practice of medicine will have become the practice of 'psychosomatic medicine.'"

the psychologic types of the persons who fall ill with such medical diseases as asthma, hypertension, arthritis, neurodermitis, colitis and peptic ulcer. The former kind of investigation is amassing an important body of data, the latter kind is intriguing and makes good reading, but to the tough minded person it is still quite unconvincing. The psychologic descriptions are too much alike, and the diseases are too obviously different.

As regards the gastrointestinal tract, Alexander [6a] believes that symptoms referable to the upper part, gastric syndromes, are encountered in persons who are active, independent and efficient; persons with colonic diarrhea are dependent, with feelings of guilt and obligation, and those with constipation are stingy, accept much and give little. Other investigators [7] find that patients with mucous colitis are meticulous, compulsive and resentful. Even ulcerative colitis has been studied from the personality standpoint [8]; patients with this disorder are said to be seclusive, apathetic and dependent. One might say that these psychologic attitudes might well be the result of the illness, especially in such a severe illness as ulcerative colitis, and have no relation to causation. Most of the investigators, however, have gone into the personality study thoroughly enough to have evidence concerning the patients' psychologic traits before they had the gastrointestinal symptoms. Moreover, many have been relieved by psychiatric treatment.

The cardiorespiratory system is, if anything, more easily affected by emotions than the gastrointestinal tract. Normal emotions are expressed by heart rate and respiration; nervousness that is so common as to be hardly classed as pathologic is shown by rapid breathing, sighing, increased ventilation, rapid and irregular heart beat. Finesinger's [9] careful studies of respiration show that the spirogram is a delicate indicator of emotional reactions. Most patients with anxiety neurosis have an irregular spirogram with many sighs; hysterical patients usually have somewhat irregular spirograms deviating from the normal, but not as greatly as those of the anxiety group. Respiratory disorders of the most severe nature, such as asthma, seem to have psychologic com-

6a. Alexander, F.: Psychoanalyt. Quart. **3**:501, 1934.

7. White, B. V.; Cobb, S., and Jones, C. M.: Mucous Colitis: A Psychological Medical Study of Sixty Cases, Psychosomatic Medicine Monograph, no. 1, Washington, D. C., National Research Council, 1939.

8. Daniels, G. E.: New England J. Med. **226**:178, 1942. Lindemann, E.: Ulcerative Colitis, read at the meeting of the Massachusetts Psychiatric Society, February 1942.

9. Finesinger, J. E.: Psychosom. Med. **2**:333, 1940.

ponents. French and Alexander and others [10] studied 27 cases of asthma intensively by psychoanalytic methods. They find that situations which tend to increase respiration, such as emotion, exertion and hurry, may bring on asthmatic attacks. Extreme emotion may stop the attack, perhaps because epinephrine is secreted into the blood stream. Many asthmatic patients were found to be excessively dependent on their mothers, and situations associated with separations from the mother often brought on attacks. Of course, the allergic aspect of the disease is given due consideration. It is not a matter of either allergy or emotions but a varying combination of the different factors. Greenhill and Finesinger [11] have found in a series of patients suffering from atopic dermatitis that exacerbation of the cutaneous lesion occurred in many cases when feelings of insecurity, hostility and depression were brought on. Saul [12] found that repressed and frustrated longing was an important factor in bringing on other kinds of allergic manifestations, such as rhinitis, edema and urticaria.

The role of the emotions in precipitating cardiac and circulatory crises has long been studied. Angina pectoris and hypertension are the commonest examples cited.

Rennie [13] believes that hypertension may be associated with protracted resentment and insecurity. Alexander [14] finds that hypertensive patients belong to the group of "overly inhibited, yet at the same time, intensely hostile and aggressive individuals."

In England the war has brought out a new crop of cases of neurocirculatory asthenia (in the last war more than 40,000 men were given pensions because of this syndrome). The pendulum has swung away from the former opinion that this was an "effort syndrome" caused by overexertion in men who were soft to the opinion that the disorder is a form of anxiety neurosis. Wood [15] has studied a large series of cases and supports the latter theory emphatically. White [16] has described the syndrome briefly and rightly separates it from "cardiac neurosis," which in his terminology is the result of frightening a person about his heart when he has a harmless murmur or an insignificant valvular lesion.

10. French, T. M.; Alexander, F., and others: Psychogenic Factors in Bronchial Asthma, Psychosomatic Medicine Monograph, nos. 1 and 2, Washington, D. C., National Research Council, 1941, vol. 2.

11. Greenhill, M. H., and Finesinger, J. E.: Neurotic Symptoms and Emotional Factors in Atopic Dermatitis, Arch. Dermat. & Syph. **46**:187 (July) 1942.

12. Saul, J.: Psychosom. Med. **3**:66, 1941.

13. Rennie, T. A. C.: New England J. Med. **221**:448, 1939.

14. Alexander, F.: Psychosom. Med. **1**:173, 1939.

15. Wood, P.: Brit. M. J. **1**:767, 805 and 845, 1941.

16. White, P. D.: Mod. Concepts Cardiovasc. Dis. **11**:8, 1942.

There are many angles to the problem of neurocirculatory asthenia that are not yet settled.

The effects of epinephrine on circulation and respiration have been mentioned. Other hormones are intimately associated with emotional states. Benedek and Rubenstein [17] have studied the correlation between ovarian activity and sex drive, fantasy and dreams. The data are all from 1 case intensively studied by endocrinologic and psychiatric methods. Although the evidence is not extensive enough to justify conclusions, a start has been made on the careful study of the relation of menstruation and emotions. Many other studies might be mentioned on arthritis, Raynaud's disease, epilepsy and hyperthyroidism. The ones discussed are from some of the more important reports published in the last three years.

DISORDERS OF THE EXTRAPYRAMIDAL SYSTEM

During the past six years a book [18] and several important papers [19] have appeared on the functions and lesions of the extrapyramidal motor system. These summarize and bring into understandable order a great mass of experimental and clinical work of the last thirty years. Twenty-five years ago textbooks gave no clue to the function of the basal ganglions and the associated nuclei in the forebrain and midbrain; some authors stated that nothing was known of the function. This is remarkable because many pertinent observations had been made during the preceding fifty years,[20] but it is a common story in the history of medicine that scattered observations are of small value until a concatenation of events focuses interest on a subject; then a great development occurs. This happened for the basal ganglions when Alzheimer (1911), Vogt (1911), Wilson (1912) and Lewy (1912) described lesions in this region corresponding to neurologic syndromes. Then the epidemic of encephalitis in 1917 to 1922 gave such a rich and dramatic demonstration of the effects of lesions of the brainstem that by 1925 the clinicopathologic pictures were recognized and referred to the extrapyramidal system, even though the physiologic implications were

17. Benedek, T., and Rubenstein, B. B.: Psychosom. Med. **1**:245 and 461, 1939.

18. Diseases of the Basal Ganglia, Proceedings of the Association for Research in Nervous and Mental Diseases (1940), Baltimore, Williams & Wilkins Company, 1942, vol. 21.

19. (*a*) Keschner, M.: Dyskinesias, Hagerstown, Md., W. F. Prior Company, Inc., 1942, vol. 10, in Tice, F.: Practice of Medicine, pp. 307-436. (*b*) Bucy, P. C.: J. Neuropath. & Exper. Neurol. **1**:224, 1942. (*c*) Putnam, T. J.: Treatment of Unilateral Paralysis Agitans by Section of Lateral Pyramidal Tract, Arch. Neurol. & Psychiat. **44**:950 (Nov.) 1940. (*d*) Myers, R.: New York State J. Med. **42**:4, 1942.

20. Hammond, W. A.: A Treatise on the Diseases of the Nervous System, New York, D. Appleton and Company, 1871.

confused. Before this there had been an "upper motor neuron" and a "lower motor neuron" to explain motor function. The new knowledge of brainstem function added so many intercalated motor neurons that the old idea no longer served. The "extrapyramidal syndromes" appeared. These are pseudobulbar paralysis, athetosis, dystonia, paralysis agitans, chorea, hepatolenticular degeneration (Wilson's disease) and pseudosclerosis. The typical forms of each are not difficult to recognize, but the etiologic agents are so various that many overlapping syndromes appear. This is especially true of a diffuse infection like encephalitis lethargica the manifestations of which simulate almost the whole list of syndromes.

To describe all these would be to write a textbook, and this has been recently well done by Keschner.[19a] For a review it is better to summarize the anatomic and the physiologic aspects and point out how lesions may interfere at different points to cause the disturbances of function one recognizes as symptoms.

BASAL GANGLIONS AND ALLIED STRUCTURES

Much difficulty is caused by the varied use of anatomic names in the study of this region. Lewy [21] has gone into the history of the nomenclature and concludes that common use at the present time makes it wise to accept the terms striatum and pallidum as signifying the two great basal ganglionic masses. There are several other nuclei nearby which are sometimes included in the term basal ganglions, the largest of these being the thalamus. The others may be said to be "peduncular" rather than "basal." Probably the best plan is to call the whole area "brainstem" [22] and speak of the different gray masses, or nuclei, of the brainstem, rather than to go into anatomic niceties that have little physiologic significance. Then the nuclei of the upper part of the brainstem, related to the extrapyramidal system, can be summarized as follows:

Nuclei of the Upper Part of the Brainstem

- Forebrain
  - Caudate nucleus
  - Lenticular nucleus
    - putamen
    - pallidum
    - striatum
  - Thalamus
  - Hypothalamus
- Midbrain
  - Subthalamic nucleus
  - Red nucleus
  - Reticular formation (upper part)
  - Substantia nigra

Figure 1, taken from a recent paper in *Medicine* by Benda and Cobb,[23] gives an idea of the relations. The brainstem is cut through the midbrain to show the red nucleus (*R. N.*) and the substantia nigra

21. Lewy, F. H.: A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:1, 1942.
22. Rioch, D. M.: A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:133, 1942.
23. Benda, C. E., and Cobb, S.: Medicine **21**:95, 1942.

(*S. N.*). The nuclei of the reticular formation (*R.*) are close to these in the midbrain and extend down into the medulla. The whole of the cut-off segment of the brainstem is moved down in the diagram for visibility; normally, it is tucked up close to the striatum and the pallidum between the temporal lobes.

PHYSIOLOGY OF THE EXTRAPYRAMIDAL SYSTEM

From 1912 to 1934 the consensus was that the function of the striatum and the pallidum had to do with "tone," "postural tone" or, more clearly stated, the taking and maintaining of postures and the control of automatic locomotor reflexes. Then the work of Bard [24] and Rioch [25] showed that the functions of these upper levels of the brainstem were more complex, had to do with highly integrated behavior patterns and could be modified by experience. Their functions resembled what one had previously considered "cortical" functions. Posture was found to be integrated much lower down the neuraxis. In the spinal cord there is little postural activity, but the more highly integrated spinal movements have simple elements of posture held for a short time if the stimulus is maintained. In the hindbrain are important postural mechanisms which cause slow and prolonged muscular responses. Chief among these is the vestibular apparatus, especially the lateral vestibular nucleus (Deiters'). This maintains a steady contraction of the antigravity muscles, holding man in the standing position. Modifications of this may be brought about by the neck reflexes which have as their afferent stimuli the proprioceptive impulses from the muscles of the neck innervated by the upper cervical and the spinal accessory nerves. Righting reflexes, that aid animals to arise and keep upright, are controlled largely from the midbrain (subthalamic nucleus, substantia nigra, red nucleus and reticular formation). For example, the eyes, working on midbrain mechanisms and in coordination with the hindbrain, set up a train of reflex events which brings a prone animal first to look up, then to sit up and then to stand, in quick and smooth sequence. The next level of the motor system lies in the striatum. Mammals with the cerebral cortex removed and the basal ganglions intact can walk, run and even jump in an effective, though automatic, way. All they seem to lack is initiative, spontaneity and memory. In other words, they have few and rudimentary conditioned reflexes and do not react in the light of past experience. Such an animal is able to go about but has no direction as to where to go except when immediate strong stimuli are applied.

24. Bard, P.: Psychol. Rev. **31**:309 and 424, 1934.
25. Rioch, D. M.: Psychiatry **1**:339, 1938.

A decorticate cat, even when the striatum is injured, can perform all the locomotor functions, so it is the peduncular nuclei rather than the striatum and the pallidum that must be concerned with simple locomotion. The function of the striatum is probably to elaborate motor behavior of even the more highly integrated types and thus make it smooth and effective. The observations of Akelaitis, von Wagenen and associates, cited by Smith and Akelaitis,[26] are pertinent here. They sectioned the corpus callosum in several cases and found no loss of motor skill. In 2 patients, both stenographers, the entire corpus callosum was cut, yet after operation they had lost none of their skill as typists, a special motor performance which needs the closest cooperation between the left and the right hand. Also among the patients was a pianist, who lost none of her skill after the operation. With the corpus callosum gone it seems that the coordination must have been carried out in the striatum or possibly even lower ganglions.

The basal ganglions may function well in decorticated mammals, but normally in human beings they are closely connected with the "extrapyramidal" part of the cerebral cortex, areas 6 and 8 of Brodman (see figure 1). Area 4 is recognized histologically by the presence of the giant pyramidal cells of Betz. The giant cells of area 4 send fibers mostly to the spinal levels of the opposite side. Stimulation of area 4 causes remarkably local contraction in small muscle groups or even single muscles. In area 6 electrical stimulation results in much more complex, slow, postural movements, involving more muscle groups. The fibers from cells in this area end mostly in area 4 and the basal gangions (fig. 1).

Cortical area 6 is the highest level of the extrapyramidal system and controls the striatum and to some extent cortical cells in area 4. Motor skills learned by means of the cortex can probably be relegated to the striatum when they become automatic. The neostriatum elaborates and smoothes out the coarser motor integrations of the paleostriatum. These in turn control the primitive walking reflexes of the subthalamic region, which make use of the righting reflexes of the midbrain nuclei and the antigravity reflexes of the hindbrain from the lateral vestibular nucleus. The lowest level is, of course, the spinal, where all the extrapyramidal impulses (running down the vestibulospinal, reticulospinal and rubrospinal tracts) reach the "motor pool" about the ventral horn cells and eventually discharge along the final common path. This summary is not entirely accurate because there are such unexplained exceptions as

26. Smith, K. V., and Akelaitis, A. J.: Studies on Corpus Callosum, Arch. Neurol. & Psychiat. **47**:519 (April) 1942.

the finding that a few "extrapyramidal" fibers come from area 6 and, joining those from area 4, travel down through the pyramids of the medulla oblongata and hence are "pyramidal."

One would not expect to have refined localization of function in such a mechanism as the basal ganglions, where the main work is probably

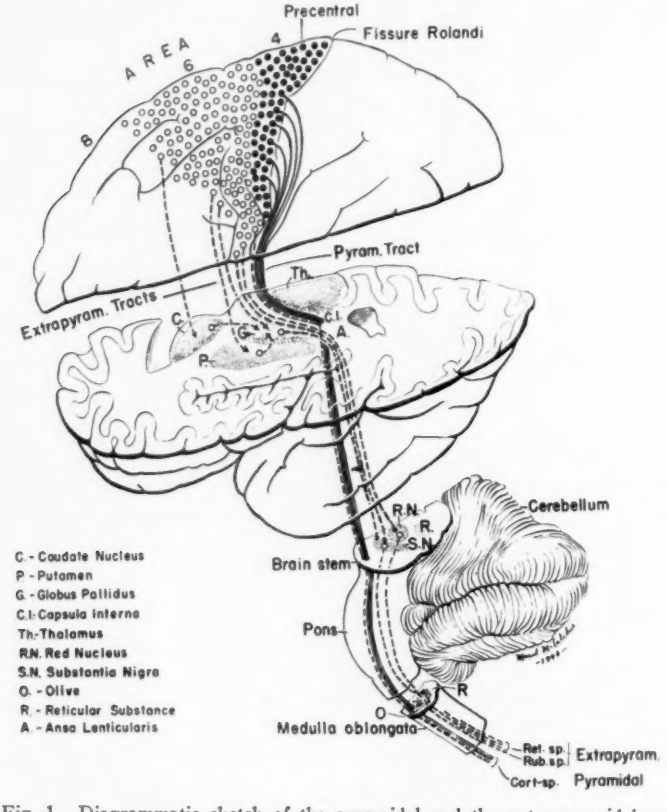

Fig. 1.—Diagrammatic sketch of the pyramidal and the extrapyramidal motor systems after Benda and Cobb.[23]

integrating, elaborating and smoothing out motor acts which vary all the way from learned skills that have become automatic to rather simple locomotor performances. The evidence from lesions sustains this expectation; localization is probably rather general in distribution; for example, the right half of the ganglionic complex controls the left half of the body. Certain symptoms appear when certain parts of the complex

are injured. When the subthalamic nucleus is affected by a focal lesion, the opposite arm and leg may show the violent, rhythmic, flail-like movements known as "ballismus." Tremor of the Parkinson type occurs when the substantia nigra, the pallidum and cortical area 6 are injured, but not destroyed, and the pyramidal tract is functioning.[23] Athetosis usually results from lesions of the striatum or the precentral cortex or both.[10b] Chorea minor probably comes from scattered petechial lesions in the striatum and the cortex, while the chronic chorea of old age has a widespread degeneration of the striatum, the pallidum and the cortex. The rigidity of paralysis agitans is sometimes laid to a lesion of the pallidum.

Of course, such observations as the foregoing ones only give a rough indication of the function. They show what the rest of the organization can and does do when a certain nucleus or group of nuclei drop out. Some clinicopathologic investigators have tried to go farther and localize more exactly the representation of the limbs and functions. At the present time the evidence does not seem to justify such refinement. Experimental work on animals has been of little help, largely because of the fact that only the higher apes have motor functions that resemble those of man.

THERAPY OF INVOLUNTARY MOVEMENTS

Of the various types of spasm and tremor the only one that appears to be amenable to reeducational training is athetosis. This may be because it occurs frequently in youth as the result of birth injury. Patient work with athetoid children over years has often made their lives much more bearable but has rarely made them self-supporting.[27]

Treatment by the use of drugs is of little value in torticollis, athetosis, torsion spasm and ballismus; it is most helpful in chorea and paralysis agitans. In chorea sedatives, such as phenobarbital, have been effective, and fever therapy seems to have been of benefit in many cases.[28] Paralysis agitans is rarely relieved by sedatives, although a combination of phenobarbital with belladonna sometimes is more beneficial than either compound alone. The best drugs for the tremor, rigidity and ocular and leg spasms of paralysis agitans are those of the atropine group. Recent experience has shown that no one alkaloid is as effective as a combination of both atropine and scopolamine. That is why extracts of belladonna root have better effects than the pure drugs. For some time

27. Carlson, E. R.: A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:534, 1942.

28. Barnacle, C. H.; Ewalt, J. R., and Ebaugh, F. G.: Artificial Fever Treatment of Chorea: Preliminary Report, J. A. M. A. **106**:2046 (June 13) 1936.

there was supposed to be a magic in the Bulgarian root, but that myth has been dispelled by the success of American products that contained both alkaloids. It is important to push the drug employed until visual disturbances and dry mouth cause one to stop; then stay at that dose until tolerance is increased, and after a week or two push the dose higher in order really to ease the rigidity and stop the tremor. Special eye glasses can be made to help vision; frequent sips of lemon juice or vinegar in water help the dry mouth. Syntropan [29] has a less toxic effect in moderate doses.

The addition of amphetamine sulfate to one of the atropine group of drugs is effective in some cases. It gives the patient more motor initiative and speeds up motor performance, as well as improving the mood. Five milligram doses administered at 7 a. m., 11 a. m. and 3 p. m. with the appropriate dose of fluidextract of belladonna root will usually suffice. The drug should not be given in excess or after 3 p. m., because of its marked effect in preventing sleep. In some cases one dose of 10 mg. on arising is better, but this compound sometimes causes a feeling of nervous tension with increased tremor and so must be avoided. Only a trial will tell which patient will be benefited.

Surgical treatment of the involuntary movements resulting from disease of the basal ganglions has taken a new start in the last five years because of the advances in knowledge of the physiology of these ganglions and their connections with the motor cortex. Horsley [30] as early as 1890 successfully extirpated part of the precentral gyrus (probably area 6) for athetosis. The cutting of the first three cervical anterior roots and the spinal accessory nerve for spasmodic torticollis is now a well recognized procedure, with good results.[31] The recent operations for athetosis, tremor and spasms, according to Putnam,[32] have

> . . . resulted in a fairly high mortality, and in many failures, but also in a gratifying number of dramatic successes. There is much reason for hoping that the worst is now over, and that the future will see indications clearly defined and procedures standardized and accepted. The urgent need for relief in the many severe cases of dystonia and parkinsonism should impel us to waste no opportunity for advance.

Myers [33] divides these surgical procedures into operations (*a*) at the level of the spinal cord, (*b*) at the level of the cerebellomesencephalic

29. Schlezinger, N. S., and Alpen, B. J.: Am. J. M. Sc. **201**:374, 1941.

30. Horsley, V.: Brit. M. J. **2**:1286, 1890.

31 Foerster, O.: Zentralbl. f. Chir. **1**:402, 1920; **2**:1106, 1920. Dandy, W. E.: Operation for Treatment of Spasmodic Torticollis, Arch. Surg. **20**:1021 (June) 1930.

32. Putnam, T. J.: A. Research Nerv. & Ment. Dis., Proc. (1920) **21**:666, 1942.

33. Myers, R.: A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:614, 1942.

complex, (*c*) at the level of the cerebral cortex and (*d*) at the level of the basal ganglions (see figure 1). Putnam [32] has cut the anterolateral or lateral tracts in the cervical portion of the spinal cord in 42 patients with athetosis. The results have been excellent in case of unilateral disease, but of the patients with bilateral athetosis, only about half have had much relief. The operative mortality has been less than 12 per cent. Putnam has tried lateral cordotomy for paralysis agitans in 7 instances. Here, as in athetosis, it is the patients with unilateral disease who were most relieved.

Operations at the cerebellomesencephalic level are particularly dangerous, and results so far do not justify this approach.

About thirty operations have been performed at the level of the basal ganglions, mostly by Myers. Parts of the caudate and the lenticular nucleus have been removed, but the most effective operation is the cutting of the fasciculus and ansa lenticularis (the main efferent pathway of the pallidum and the striatum) as they pass near the foramen of Monro beneath the floor of the lateral ventricle (see figure 1). The approach is through an incision in the frontal lobe that exposes the floor of the lateral ventricle and the foramen of Monro. Several patients have been remarkably improved by this procedure, even those with bilateral involvement who have had bilateral operations. Unfortunately, the patients are usually poor "operative risks," the operation is difficult and the mortality is about 20 per cent. Obviously, the physiologic approach is correct, but Myers himself believes the operative procedure needs refinement before it should be continued. Extirpations at the cortical level (areas 4 or 6, separately or combined) have been performed for athetosis and paralysis agitans. The patients with unilateral symptoms, especially those with conditions of traumatic origin, have usually been relieved.[34] In patients with degenerative disease of both hemispheres, double athetosis and Parkinson's disease, the results are more dubious and the mortality is high, over 17 per cent.[35]

One must conclude that at present the operative treatment of involuntary movements is experimental. Much headway has been made; much has been learned about the physiologic and pathologic aspects, and the prospects are bright that in the not far distant future surgical intervention will make a great contribution to the treatment of athetosis, tremor, rigidity, torsion spasm, ballismus and chorea, as it has already done for torticollis and the rare cases of unilateral dyskinesia. It must be

34. Bucy, P. C.: A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:551, 1942.

35. Klemme, R. M.: A. Research Nerv. & Ment. Dis., Proc. (1940) **21**:596, 1942.

acknowledged, however, that up to the present no relatively simple and safe operation has been devised that offers adequate hope of relief of symptoms.

ELECTROENCEPHALOGRAPHY

Since 1935, when the very beginnings of clinical electroencephalography were mentioned in this review, conspicuous advance has been made. Now many large hospitals are equipped to make electroencephalographic records ("brain waves"), and in certain spheres of neurology the technic has become an important diagnostic aid. The fine atlas of Gibbs and Gibbs [5] already mentioned is an extensive study, showing that an abnormal electroencephalogram accompanies most lesions of the cerebrum and some disorders in which lesions are not evident at autopsy. The brain wave pattern, however, is not characteristic for any disease, with the exception of the bursts of wave-spike formations frequently seen in epilepsy, usually in petit mal. This fact, however, does not nullify the usefulness of the electroencephalogram as a diagnostic instrument. Often one wishes to know whether certain symptoms are caused by cerebral lesions or are due to neurotic or psychotic disorders without lesions. For example, a differential diagnosis between schizophrenic stupor and coma due to brain tumor would be possible. Again, a hysterical fit can be differentiated from an epileptic seizure if one is careful to rule out the fast high waves caused by movements of muscle.

Localization of cerebral lesions can also be made electrically with a fair degree of accuracy. As many as twenty-four leads can be placed on the skull, and by a triangulation survey the point from which the abnormal waves seem to originate can often be found. This is especially useful in studying tumors and traumatic lesions and in deciding whether an epilepsy is focal and perhaps approachable by surgical therapy.

In psychiatry the electroencephalogram is of some diagnostic help. Manic-depressive and schizophrenic patients often show irregular unstable patterns,[36] but they are far from pathognomonic; some normal people show them also. Possibly phlegmatic persons show more alpha waves (about 10 per second activity over the occipital lobes), and tense, anxious persons show more rapid, small (beta) waves (see figure 2). Problem children in whom encephalopathy or epilepsy was not suspected can often be proved to be suffering from one or both of these conditions by the finding of long, slow (delta) waves. These occur normally in infancy or in deep sleep but are distinctly pathologic in children over 8 years of age who are awake.

36. Pacella, B. L., and Barerra, S. E.: Psychiatric Quart. **15**:407, 1941.

Epileptic brain waves have been extensively studied, especially by Gibbs, Gibbs and Lennox [37] and by Jasper, in a chapter in a book by Penfield and Erickson.[1] The essential abnormalities are the great magnitude and the episodic nature of the discharges. The waves are large (high voltage) and come in bursts, whether they are long slow delta waves, rapid high spikes or wave-spike combinations. Epilepsy is so varied in its phenomena that there is no definite correspondence between the different types of seizure and the different sorts of epileptic wave pattern, with the exception of the common finding of bursts of wave-spike combinations in the short lapses known as petit mal. The electroencephalogram is useful not only for the diagnosis of epilepsy but in the treatment of epilepsy,

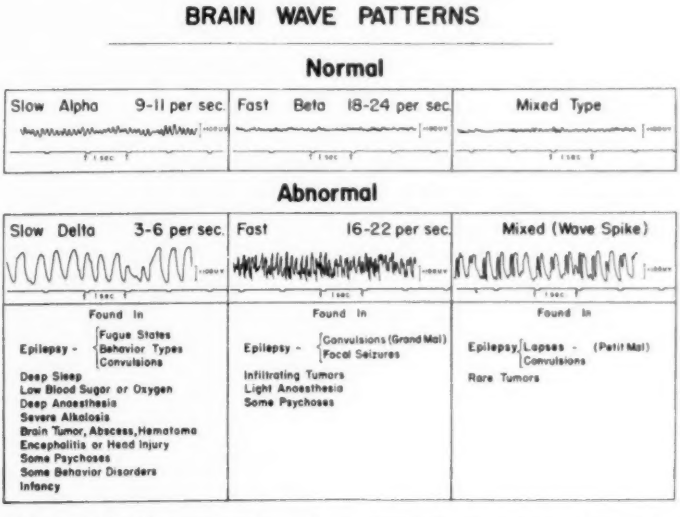

Fig. 2.—Schwab's [39] comparison of the more common patterns of normal and abnormal brain waves. In the abnormal group epilepsy gives the highest voltages (biggest "waves"), and they come in attacks. Sleep, coma, tumor, encephalitis, etc., are likely to have more continuous abnormal waves of less extreme voltage. Of course, the long, slow waves of sleep are a normal phenomenon and are classed under "abnormal" on the chart only because such waves would be very abnormal if produced by a person during a regular electroencephalographic test while awake.

because the effect of drugs may be followed by making repeated electroencephalograms and seeing which drug has the most effect in smoothing

37. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Cerebral Dysrhythmias of Epilepsy: Measures for Their Control, Arch. Neurol. & Psychiat. **39**:298 (Feb.) 1938.

out the abnormal waves. In this way many weeks or months may be saved because the clinical observation of epileptic patients is a long, drawn-out affair.

Lennox [2] calls epilepsy "paroxysmal cerebral dysrhythmia." From the electroencephalographic point of view this is a good description and saves one from using the socially inacceptable word "epilepsy." An abnormal shower of brain waves, however, does not cause an epileptic fit, any more than abnormal electrocardiographic waves cause angina pectoris. If one wishes to speak accurately about causation, it is necessary to go back to some processes behind both the fit and the dysrhythmia. The nerve impulse and the electrical change in potential (registered as a brain wave) are not identical. Just what the nerve impulse may be is not yet known, but it is a physiologic process with characteristics quite different from an electrical current. The brain, when functioning, produces changes in electrical potential, and these are recorded in the electroencephalogram, but this is not a record of nerve impulses. Some disorganization of the nerve impulses precipitates both the clinical fits seen and the brain waves registered. The ultimate cause is physiochemical and is unknown.

Davis [38] has reviewed the uses of the electroencephalogram, and Schwab [39] has emphasized the main types of abnormality and their similarities to normal electroencephalographic phenomena. His diagram is reproduced here. Schwab's emphasis is a good corrective for the too prevalent idea that now the diagnosis of neuropsychiatric disorders is made easy because abnormal brain waves are differentially diagnostic.

Briefly stated, the electroencephalogram can record gross disorders of the function of the brain; the subtler changes are not shown or at least are not yet recognized. The abnormal brain waves can often be correlated with clinical and with autopsy data. This makes it probable that the abnormal waves are frequently related to cerebral lesions, but physiologically speaking, the electroencephalogram registers only functional changes in the brain.

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38. Davis, H.: Electroencephalography, J. A. M. A. **117**:983 (Sept. 20) 1941.
39. Schwab, R. S.: M. Clin. North America **25**:1477, 1941.

OBESITY

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DEFINITION

Obesity is that condition in which the body contains an abnormally large amount of adipose tissue. The excessive fat may be evenly distributed or may be present to a much greater extent in some regions than in others. When the accumulation is sharply localized to one or more discrete encapsulated masses, one speaks of "lipomatosis" in contradistinction to "obesity."

WEIGHT

Since the accumulation of adipose tissue causes a corresponding increase in weight, much effort has been directed toward establishing a weight which is best in regard to longevity and mental and physical fitness.

Normal Weight.—The Child Health Association has compiled tables (tables 1 through 4) that give the average weight for height and sex of large numbers of healthy children from birth through the age of 18 years. These tables are widely accepted as the most satisfactory standards.

However, Fisk [1] has shown that the average weights of persons over 30 years of age are too great as judged by life expectancy and has found that the average weight at 30 is the most desirable weight for the remainder of the life. Table 5, compiled by Fisk, is based on that principle. The heights include shoes, and the weights, clothes and food.

Departures from these standards are sometimes condoned because of supposedly heavy bones, excessive muscular development or hereditary type, but according to Fisk, "Life insurance experience has shown that heavyweights, regardless of type and heredity, show an extra mortality."

Hazard of Overweight.—Dublin and Lotka [2] have analyzed the influence of weight on the duration of life of 192,304 men aged 21 years

1. Fisk, E. L.: Health Building and Life Extension, New York, The Macmillan Company, 1923.

2. Dublin, L. I., and Lotka, A. J.: Length of Life, New York, The Roland Press Co., 1936.

or over when accepted for life insurance. The deaths per hundred thousand, age being disregarded, are given in table 6.

Dublin and Lotka concluded that "the penalty of overweight is one-fourth to three-fourths excess in mortality." These studies become still more informative when they are related to age, since excessive weight carries a much greater risk in persons beyond 45 years of age than earlier (table 7). How great the risk is for the important years from 45 to 50 appears dramatically in table 8. It is startling to learn

TABLE 1.—*Weights of Girls from Birth to School Age*

Height, In.	Weight, Lb.											
	1 Mo.	3 Mo.	6 Mo.	9 Mo.	12 Mo.	18 Mo.	24 Mo.	30 Mo.	36 Mo.	48 Mo.	60 Mo.	72 Mo.
20	8	..	..	..	..	..	..	..	..	..	..	..
21	9	10	..	..	..	..	..	..	..	..	..	..
22	10	11	..	..	..	..	..	..	..	..	..	..
23	11	12	13	..	..	..	..	..	..	..	..	..
24	12	13	14	14	..	..	..	..	..	..	..	..
25	13	14	15	15	..	..	..	..	..	..	..	..
26	..	15	16	17	17	..	..	..	..	..	..	..
27	..	16	17	18	18	..	..	..	..	..	..	..
28	..	..	19	19	19	19	..	..	..	..	..	..
29	..	..	19	20	20	20	..	..	..	..	..	..
30	..	..	21	21	21	21	21	..	..	..	..	..
31	..	..	..	22	22	23	23	23	..	..	..	..
32	..	..	..	..	23	24	24	24	25	..	..	..
33	..	..	..	..	..	25	25	25	26	..	..	..
34	..	..	..	..	..	26	26	26	27	..	..	..
35	..	..	..	..	..	29	29	29	29	29	..	..
36	..	..	..	..	..	..	30	30	30	30	31	..
37	..	..	..	..	..	..	31	31	31	31	32	..
38	..	..	..	..	..	..	..	33	33	33	33	..
39	..	..	..	..	..	..	..	34	34	34	34	34
40	..	..	..	..	..	..	..	..	35	36	36	36
41	..	..	..	..	..	..	..	..	..	37	37	37
42	..	..	..	..	..	..	..	..	..	39	39	39
43	..	..	..	..	..	..	..	..	..	40	41	41
44	..	..	..	..	..	..	..	..	..	..	42	42
45	..	..	..	..	..	..	..	..	..	..	..	45
46	..	..	..	..	..	..	..	..	..	..	..	47
47	..	..	..	..	..	..	..	..	..	..	..	50
48	..	..	..	..	..	..	..	..	..	..	..	52

that a mere 25 pounds (11 Kg.) of extra weight lessens one's life expectancy by 25 per cent. Fisk found likewise that persons in full middle life who weigh 20 pounds (9 Kg.) more than the average instead of 10 pounds (4.5 Kg.) less are incurring an extra 25 per cent risk. In another place he pointed out that "fifty pounds overweight at age forty-five imposes as much extra mortality as valvular heart disease."

ETIOLOGY OF OBESITY

Is There a Disorder of the Utilization of Energy?—Because of the prevalence of the belief that some patients gain weight even though they do not overeat and that others do not lose when they are underfed,

there has been a continued search for some metabolic aberration in this disease.

Basal Metabolism.—Early students found that pound for pound obese persons produce less heat in the resting postabsorptive state than do normal controls. Had they made the comparison on the basis of height, they would have found that the heat production of obese persons was greater than normal. But Rubner, Lusk and others have demonstrated that the basal heat production of all mammals is proportional to

TABLE 2.—*Weights of Boys from Birth to School Age*

Height,	Weight, Lb.											
In.	1 Mo.	3 Mo.	6 Mo.	9 Mo.	12 Mo.	18 Mo.	24 Mo.	30 Mo.	36 Mo.	48 Mo.	60 Mo.	72 Mo.
20	8	..	..	..	..	..	..	..	..	..	..	..
21	9	10	..	..	..	..	..	..	..	..	..	..
22	10	11	..	..	..	..	..	..	..	..	..	..
23	11	12	13	..	..	..	..	..	..	..	..	..
24	12	13	14	..	..	..	..	..	..	..	..	..
25	13	14	15	16	..	..	..	..	..	..	..	..
26	..	15	17	17	18	..	..	..	..	..	..	..
27	..	16	18	18	19	..	..	..	..	..	..	..
28	..	..	19	19	20	20	..	..	..	..	..	..
29	..	..	20	21	21	21	..	..	..	..	..	..
30	..	..	22	22	22	22	22	..	..	..	..	..
31	..	..	..	23	23	23	23	24	..	..	..	..
32	..	..	..	24	24	24	25	25	..	..	..	..
33	..	..	..	..	26	26	26	26	26	..	..	..
34	..	..	..	..	..	27	27	27	27	..	..	..
35	..	..	..	..	..	29	29	29	29	29	..	..
36	..	..	..	..	..	..	30	31	31	31	..	..
37	..	..	..	..	..	..	32	32	32	32	32	..
38	..	..	..	..	..	..	..	33	33	33	34	..
39	..	..	..	..	..	..	..	35	35	35	35	..
40	..	..	..	..	..	..	..	..	36	36	36	36
41	..	..	..	..	..	..	..	..	..	38	38	38
42	..	..	..	..	..	..	..	..	..	39	39	39
43	..	..	..	..	..	..	..	..	..	41	41	41
44	..	..	..	..	..	..	..	..	..	..	43	43
45	..	..	..	..	..	..	..	..	..	..	45	45
46	..	..	..	..	..	..	..	..	..	..	..	48
47	..	..	..	..	..	..	..	..	..	..	..	50
48	..	..	..	..	..	..	..	..	..	..	..	52
49	..	..	..	..	..	..	..	..	..	..	..	52

the surface area of the body and that no such relation exists when either weight or height alone is used as the basis of comparison.

Benedict, using the statistical method, has published tables by which one can predict the basal metabolic rate of normal persons on the basis of age, height and weight. His values closely approximate those calculated by the surface area method. There is, then, no doubt about the range of basal heat production of normal adults.

Subsequently, Boothby and Sandiford [3] measured basal heat production in 94 obese patients and found that in 81 per cent of them the rates

3. Boothby, W. M., and Sandiford, I.: J. Biol. Chem. **54**:783, 1922.

were within 10 per cent of the normal heat production per square meter. In 3 instances the rates fell between —16 and —20 per cent, and another patient produced heat at a rate more than 16 per cent above normal.

Strouse, Wang and Dye [4] compared the basal metabolic rates of normal persons with those of subjects who were underweight and over-

TABLE 3.—*Weights of Girls from Five to Eighteen Years*

Height, In.	Weight, Lb.													
	5 Yr.	6 Yr.	7 Yr.	8 Yr.	9 Yr.	10 Yr.	11 Yr.	12 Yr.	13 Yr.	14 Yr.	15 Yr.	16 Yr.	17 Yr.	18 Yr.
38	33	33	..	..	..	..	..	..	..	..	..	..	..	..
39	34	34	..	..	..	..	..	..	..	..	..	..	..	..
40	36	36	36	..	..	..	..	..	..	..	..	..	..	..
41	37	37	37	..	..	..	..	..	..	..	..	..	..	..
42	39	39	39	..	..	..	..	..	..	..	..	..	..	..
43	41	41	41	41	..	..	..	..	..	..	..	..	..	..
44	42	42	42	42	..	..	..	..	..	..	..	..	..	..
45	45	45	45	45	45	..	..	..	..	..	..	..	..	..
46	47	47	47	48	48	..	..	..	..	..	..	..	..	..
47	49	50	50	50	50	50	..	..	..	..	..	..	..	..
48	..	52	52	52	52	53	53	..	..	..	..	..	..	..
49	..	54	54	55	55	56	56	..	..	..	..	..	..	..
50	..	56	56	57	58	59	61	62	..	..	..	..	..	..
51	..	..	59	60	61	61	63	65	..	..	..	..	..	..
52	..	..	63	64	64	64	65	67	..	..	..	..	..	..
53	..	..	66	67	67	68	68	69	71	..	..	..	..	..
54	..	..	..	69	70	70	71	71	73	..	..	..	..	..
55	..	..	..	72	74	74	74	75	77	78	..	..	..	..
56	..	..	..	..	76	78	78	79	81	83	..	..	..	..
57	..	..	..	..	80	82	82	82	84	88	92	..	..	..
58	..	..	..	..	..	84	86	86	88	93	96	101	..	..
59	..	..	..	..	..	87	90	90	92	96	100	103	104	..
60	..	..	..	..	..	91	95	95	97	101	105	108	109	111
61	..	..	..	..	..	..	99	100	101	105	108	112	113	116
62	..	..	..	..	..	..	104	105	106	109	113	115	117	118
63	..	..	..	..	..	..	..	110	110	112	116	117	119	120
64	..	..	..	..	..	..	..	114	115	117	119	120	122	123
65	..	..	..	..	..	..	..	118	120	121	122	123	125	126
66	..	..	..	..	..	..	..	..	124	124	125	128	129	130
67	..	..	..	..	..	..	..	..	128	130	131	133	133	135
68	..	..	..	..	..	..	..	..	131	133	135	136	136	138
69	..	..	..	..	..	..	..	..	..	135	137	138	140	142
70	..	..	..	..	..	..	..	..	..	136	138	140	142	144
71	..	..	..	..	..	..	..	..	..	138	140	142	144	145

weight. Per square meter of body surface they found practically no differences.

Among 180 cases of extreme obesity Grafe [5] found only 3 in which there was a definite decrease in basal metabolic rate.

4. Strouse, S.; Wang, C. C., and Dye, M.: Studies on Metabolism of Obesity: Basal Metabolism, Arch. Int. Med. **34**:275 (Sept.) 1924.

5. Grafe, E.: Metabolic Diseases and Their Treatment, translated by M. G. Boise, Philadelphia, Lea & Febiger, 1933.

TABLE 4.—*Weights of Boys from Five to Nineteen Years*

Height, In.	Weight, Lb.														
	5 Yr.	6 Yr.	7 Yr.	8 Yr.	9 Yr.	10 Yr.	11 Yr.	12 Yr.	13 Yr.	14 Yr.	15 Yr.	16 Yr.	17 Yr.	18 Yr.	19 Yr.
38	34	34	..	..	..	..	..	..	..	..	..	..	..	..	..
39	35	35	..	..	..	..	..	..	..	..	..	..	..	..	..
40	36	36	..	..	..	..	..	..	..	..	..	..	..	..	..
41	38	38	38	..	..	..	..	..	..	..	..	..	..	..	..
42	39	39	39	39	..	..	..	..	..	..	..	..	..	..	..
43	41	41	41	41	..	..	..	..	..	..	..	..	..	..	..
44	44	44	44	44	..	..	..	..	..	..	..	..	..	..	..
45	46	46	46	46	46	..	..	..	..	..	..	..	..	..	..
46	47	48	48	48	48	..	..	..	..	..	..	..	..	..	..
47	49	50	50	50	50	50	..	..	..	..	..	..	..	..	..
48	..	52	53	53	53	53	..	..	..	..	..	..	..	..	..
49	..	55	55	55	55	55	56	..	..	..	..	..	..	..	..
50	..	57	58	56	56	58	58	58	..	..	..	..	..	..	..
51	..	..	61	61	61	61	61	61	..	..	..	..	..	..	..
52	..	..	63	64	64	64	64	64	64	..	..	..	..	..	..
53	..	..	66	67	67	67	67	68	68	..	..	..	..	..	..
54	..	..	..	70	70	70	70	71	71	72	..	..	..	..	..
55	..	..	..	72	72	73	73	74	74	74	..	..	..	..	..
56	..	..	..	75	76	77	77	77	78	78	80	..	..	..	..
57	..	..	..	..	79	80	81	81	82	83	83	..	..	..	..
58	..	..	..	..	83	84	84	85	85	86	87	..	..	..	..
59	..	..	..	..	..	87	88	89	89	90	90	90	..	..	..
60	..	..	..	..	..	91	92	92	93	94	95	96	..	..	..
61	..	..	..	..	..	..	96	96	97	99	100	103	106	..	..
62	..	..	..	..	..	..	100	101	102	103	104	107	111	116	..
63	..	..	..	..	..	..	105	106	107	108	110	113	118	123	127
64	..	..	..	..	..	..	..	109	111	113	115	117	121	126	130
65	..	..	..	..	..	..	..	114	117	118	120	122	127	131	134
66	..	..	..	..	..	..	..	..	119	122	125	128	132	136	139
67	..	..	..	..	..	..	..	..	124	128	130	134	136	139	142
68	..	..	..	..	..	..	..	..	..	134	134	137	141	143	147
69	..	..	..	..	..	..	..	..	..	137	139	143	146	149	152
70	..	..	..	..	..	..	..	..	..	143	144	145	148	151	155
71	..	..	..	..	..	..	..	..	..	148	150	151	152	154	159
72	..	..	..	..	..	..	..	..	..	...	153	155	156	158	163
73	..	..	..	..	..	..	..	..	..	...	157	160	162	164	167
74	..	..	..	..	..	..	..	..	..	...	160	164	168	170	171

TABLE 5.—*Ideal Weights of Men and Women* *

Men			Women		
Height		Weight, Lb.	Height		Weight, Lb.
Ft.	In.		Ft.	In.	
5		126	4	8	112
5	1	128	4	9	114
5	2	130	4	10	116
5	3	133	4	11	118
5	4	136	5		120
5	5	140	5	1	122
5	6	144	5	2	124
5	7	148	5	3	127
5	8	152	5	4	131
5	9	156	5	5	134
5	10	161	5	6	138
5	11	166	5	7	142
6		172	5	8	146
6	1	178	5	9	150
6	2	184	5	10	154
6	3	190	5	11	157
6	4	196	6		161
6	5	201			

* Adapted from Mak.[1]

The occasional moderately low rate (from —15 to —25 per cent) exhibited by an obese person does not contribute to the understanding of obesity, since equally low rates are encountered as frequently among healthy persons.

The few obese persons whose basal metabolic rate is low enough to be definitely pathologic will be found to be suffering from some

TABLE 6.—*Influence of Weight on Mortality; Deaths per Hundred Thousand Men Accepted for Insurance*

Weight	Deaths
Standard	844
Underweight, total	848
Overweight, total	1,111
Underweight, 5-14%	833
Underweight, 15-34%	913
Overweight, 5-14%	1,027
Overweight, 15-24%	1,215
Overweight, 25% or more	1,472

TABLE 7.—*Influence of Weight on Mortality as Modified by Age, Deaths per Hundred Thousand*

Weight	Age, Yr.	
	Under 45	Over 45
Standard	463	1,308
Underweight, total	498	1,274
Overweight, total	527	1,824

TABLE 8.—*Influence of Overweight on Mortality in Persons Aged 45 to 50 Years*

Pounds Overweight	Increase in Death Rate Over Average, %
10	8
20	18
30	28
40	45
50	56
60	67
70	91
90	116

disease in which adiposity is a complication or an unrelated accompaniment and not the primary abnormality. Myxedema is the most frequent of the diseases characterized by low metabolic rates. A discussion of its relation to weight will be found on pages 1058 to 1073.

These and many other studies lend overwhelming support to the statement that obesity is not caused by lessened expenditure of energy in the basal state. In fact, an obese person produces more heat than a normal person of corresponding age, height and sex. While both will

produce the same number of calories per square meter of body surface per unit of time, the obese person has a larger surface, and therefore the total heat produced by the obese person in the basal state is greater actually than the total basal heat produced by the normal person.

Strang and Evans [6] made careful measurements of the basal metabolic rates of 5 obese women, and the average values are compared in table 9 with the predictions for a normal woman of the same average age.

In order to emphasize the large expenditure of energy of an obese person in the basal state the authors gave the following hypothetic example: An obese woman aged 49, 5 feet (152 cm.) tall, weighs 294 (133 Kg.) pounds. Her surface area accordingly will be 2.2 square meters. Her heat production will be 77 calories per hour. In order to produce the same amount of heat in the basal state a normal man of the same age would have to be 6 feet 1 inch (185 cm.) tall.

Specific Dynamic Effect.—If the heat production of a person who has been without food for twenty hours and who has been reclining

TABLE 9.—*Total Basal Heat Production (Calories) of Five Obese Women Compared With Ideal Values*

	Weight, Lb.	Surface Area, Sq. M.	Calories/Sq. M./Hr.	Total No. of Calories/Hr.
Ideal	129	1.59	36.5	58
Observed	238	2.06	35.5	73

quietly and comfortably for a half hour (basal state) is carefully measured and he is then fed, he will shortly produce more heat per unit of time than he did in the fasting state. This response is not caused by digestion or absorption, since it is equally great after the intravenous injection of dextrose or some of the amino acids that result from the digestion of protein. The extra heat amounts to 200 to 300 calories in the ensuing twenty-four hours. If some metabolic fault prevented or greatly lessened this specific response to food, the person so afflicted would gain weight, provided he continued to partake of the same amount and the same kind of food and provided he did not increase his activity. His appetite might, however, direct him to eat less, since he needed less, and in that case his weight would not increase. Several students, without making any allowance for the second alternative, have attributed obesity to lessened specific dynamic effect of food.

Many attempts have been made to show that the caloric response to food is controlled by the hypophysis. Thus Plaut [7] stated, as a result of her studies, that a normal basal metabolic rate, coupled with a

6. Strang, J. M., and Evans, F. A.: J. Clin. Investigation **6**:277, 1928.

7. Plaut, R.: Deutsches Arch. f. klin. Med. **139**:285, 1922.

lowered specific dynamic response to protein, is characteristic of disease of the hypophysis. Using these criteria, she expressed the belief that she [8] was able to show that in certain cases obesity was caused by hypofunction of the pituitary. Kestner, Knipping and Liebesny subsequently published many determinations that seemed to confirm her work. The technic employed by these investigators has been criticized by a number of workers. Dürr,[9] for example, pointed out that a normal person exhibited no response to food in three hours and a response of only 18 per cent in five hours. Lauter [10] in careful studies found that the specific dynamic response of normal subjects varies so widely that only its total absence is of diagnostic significance. Gaebler,[11] working in Lusk's laboratory, found that dogs from which the hypophysis had been removed responded normally to a standard protein meal.

Because of the disagreement Johnston [12] reinvestigated this question. She restricted her studies to patients in whom destructive diseases of the pituitary were demonstrated, usually by operation or at autopsy. She obtained large responses in all cases (18 to 28 per cent), and pointed out that it was not possible to secure uniform results in human beings. She found it impossible to obtain a consistent response to sucrose or aminoacetic acid in a normal subject maintained on a constant diet. This again emphasized the caution with which small responses must be interpreted.

Later work suggests that the liver is responsible for the increased heat liberated during the metabolism of protein. Bollman and Magath [13] showed that deaminization took place in the liver, and later, Wilhelmj and Mann [14] found that administration of amino acids to hepatectomized dogs did not increase the heat production. Finally, Dock,[15] by excluding various portions of the bodies of rats from the circulation, found that at least 85 per cent of the specific dynamic heat was liberated in the abdominal viscera. He concluded that at least 80 per cent of the specific effect is due to the increased heat produced by the hepatic cells during protein digestion.

The relation of the specific dynamic effect to the obese state has been studied so painstakingly and comprehensively by Strang and McClugage [16] that their results may be accepted with great confidence. They emphasized that the base line, that is, the value of the basal metabolism, is the most important feature of the test. Earlier workers

8. Plaut, R.: Deutsches Arch. f. klin. Med. **142**:266, 1923.
9. Dürr, R.: Klin. Wchnschr. **4**:1496, 1925.
10. Lauter, S.: Deutsches Arch. f. klin. Med. **150**:315, 1926.
11. Gaebler, O. H.: J. Biol. Chem. **81**:41, 1929.
12. Johnston, M. W.: J. Clin. Investigation **11**:437, 1932.
13. Bollman, J. L., and Magath, T. B.: Am. J. Physiol. **78**:258, 1926.
14. Wilhelmj, C. M., and Mann, F. C.: S. Clin. North America **9**:829, 1929.
15. Dock, W.: Am. J. Physiol. **97**:117, 1931.
16. Strang, J. M., and McClugage, H. B.: Am. J. M. Sc. **182**:49, 1931.

have failed to train their subjects sufficiently. Strang and McClugage have repeated basal determinations until uniform results were obtained. In order to make a test acceptable they demanded that the basal calories on the test day must vary less than 2 calories from the average of measurements within fourteen days. On this basis they rejected ten of their twenty-five determinations. They pointed out the fallacy of the usual way of expressing the specific effect as a percentage of the basal calories. For example, a 10 calory increase attributable to food when the subject is producing 60 calories per hour in the basal state is an increase of 16 per cent, but the same specific increment with a basal heat production of 90 calories is an increase of only 11 per cent. Since obese persons produce more heat in the basal state than do normal persons, the same absolute response to a test diet may appear to be low in obese persons when the percentile method of comparison is used.

It is likewise misleading to express the response to a test diet in terms of surface area. Thus an increment of 10 calories due to food in a person whose surface area is 1.67 square meters gives an increase

TABLE 10.—*Specific Dynamic Effect of Food*

Type of Subject	Individual Variation in No. of Calories	Average No. of Calories
Normal	43 to 61	51
Obese	44 to 74	58
Thin	59 to 78	67

of 6 calories per square meter, whereas if the surface were 2.2 square meters, as is common in obese persons, the increase would be only 4.5 calories per square meter. Hence, the same absolute increase in the heat results in an apparent depression for obese subjects.

These workers emphasized the irregularity of the response to food when viewed from hour to hour and were in agreement with Benedict and Carpenter [17] that a true appreciation of the thermal effect of a meal is obtained by focusing the attention on the total increment.

With these considerations in mind, Strang and McClugage studied 5 normal, 5 thin and 8 obese persons. The total increment for the eight hours following the ingestion of the test meal will be found in table 10.

These studies have been described in considerable detail with the hope of convincing the reader that the acquisition of adiposity cannot be attributed to a lessened specific dynamic effect of food.

Luxuskonsumption.—Grafe and Graham [18] have maintained that in addition to the specific dynamic response, which comes to an end in

17. Benedict, F. G., and Carpenter, T. M.: Food Ingestion and Energy Transformations with Special Reference to the Stimulating Effect of Nutrients, Publication 216, Carnegie Institution of Washington, 1918.

18. Grafe, E., and Graham, D.: Ztschr. f. physiol. Chem. **73**:1, 1911.

twelve hours or less, the heat production of the organism throughout the twenty-four hours is influenced by the quantity of food eaten. Leaving the increases that accompany activity and the specific dynamic effect out of consideration, they expressed the belief that the intensity of the metabolism is stimulated by generous (excessive) feeding and depressed by meager supplies of food. Such a mechanism would tend to maintain constancy of weight. Obesity would develop when the mechanism failed to respond to overeating, and leanness would be the result of abnormally great responses.

Grafe expressed the belief that he has demonstrated the existence of this mechanism by recording the heat production in the resting fasting state following various types of feeding. He denied that the basal metabolic rate of an animal is predictable from its surface area because it is significantly affected by the calorific value of the food previously ingested. He thus set aside the classic experiments of Rubner, Lusk, Benedict and many others, who have shown that all mammals produce heat at approximately the same rate per square meter of body surface when they are in the basal state. This generalization has been refined for the human being, for whom it has been established that slight modifications need to be made for age and sex. Many thousands of determinations have proved that the basal heat production per square meter per hour by a normal person can be predicted with great accuracy without any knowledge of what he has been eating during the preceding days.

It has also been well established that the basal oxidative rate is greatly depressed by prolonged severe underfeeding. Zuntz,[19] for example, showed that the decrease might amount to as much as 30 per cent of the normal value. The organism does then possess a mechanism that retards the destruction of body tissues when it has to contend with starvation. But this phenomenon seems to bear no relation to Grafe's concept that the lean organism is so because it overoxidizes an otherwise adequate supply of food or that adiposity represents underoxidation. It should be recalled that the careful studies of Boothby and Sandiford [3] have demonstrated that the basal metabolic rate of an obese person is normal.

Grafe and Koch [20] reported a study on a patient whose normal weight was 62.6 Kg. and whose height was 156 cm. Because of stenosis of the pylorus accompanied by persistent vomiting his weight had fallen to 40 Kg. In this emaciated condition he produced 30 calories per square meter per hour in the resting fasting state. The prediction for a man of his age and height and of normal weight is 39 calories per square meter. Relief of the stenosis and subsequent feeding of 100

19. Zuntz, N.: Biochem. Ztschr. **55**:341, 1913.

20. Grafe, E., and Koch, R.: Deutsches Arch. f. klin. Med. **106**:564, 1912.

calories per kilogram brought his weight up to 60 Kg. He then produced 40.7 calories per square meter, which was within 3 per cent of the prediction for a man of his age and height and of normal weight. This study merely confirmed Schöndorff's [21] earlier work that starvation depressed the basal metabolism. Grafe did not present any data to support his contention that continued superalimentation was capable of causing the oxidations to proceed at a rate greater than normal.

The reader will recall that Grafe had said that the normal organism maintains a constant weight in spite of overfeeding because the extra food stimulates the total metabolism to such an extent that the excess is oxidized, but he did not publish any data that dealt with total heat production throughout the twenty-four hours. In order to test Grafe's postulate, Wiley and Newburgh [22] studied the responses of a thin person by means of a method [23] recently developed by them for determining the total heat production for any desired length of time.

The subject was 28 years old, 6 feet (183 cm.) tall and weighed 45 pounds (20 Kg.) less than normal. For the first eighteen days he was fed a constant diet that yielded 2,922 calories daily. During this same period the twenty-four hourly heat production averaged 2,947 calories. His weight at the beginning was 57,562 Gm., and at the end it was 57,548 Gm. He was then fed a diet that yielded 4,755 calories daily. This was an increase of 1,833 calories. During the fifteen days the latter diet was taken the subject gained 4,410 Gm. (nearly 10 pounds). Heat production per twenty-four hours in the second period averaged 3,082 calories. Accordingly, he produced 135 more calories when he was ingesting about 5,000 calories than when he took about 3,000 calories, an increase of 4.5 per cent in total metabolism. The increase in the surface area that accompanied the increase in weight accounted for 68 extra calories and the additional carbohydrates and fat could be expected to increase the specific dynamic effect of the second diet by 85 calories, according to a calculation by Lusk.[24] Accordingly, the predicted increase in heat production during the second period without recourse to *Luxuskonsumption* is 153 calories, whereas the actual increase was only 135 calories. When the subject was partaking of the smaller diet, the fasting resting heat production was at the rate of 35.5 calories per square meter per hour. At the end of the period of overfeeding he produced 36.9 calories under the same conditions. The difference of 1.4 calories is not significant. There is, then, no evidence that either the basal or the total metabolism was stimulated by superalimentation.

21. Schöndorff, B.: Arch. f. d. ges. Physiol. **67**:430, 1912.

22. Wiley, F. H., and Newburgh, L. H.: J. Clin. Investigation **10**:733, 1931.

23. This method is described in the section dealing with the total metabolism of obese persons. See page 1045.

24. Lusk, G.: J. Nutrition **3**:519, 1931.

Total Metabolism.—It has repeatedly been observed that some obese patients who are receiving only minimal quantities of food fail to lose weight. Von Noorden [25] reported such experiences many years ago. More recently Grafe [5] has published several striking examples, one of which is reproduced here in part.

The patient, aged 38, was 5 feet, 4 inches (163 cm.) tall and weighed 378 pounds (171 Kg.). She became stout at 10 years of age. When she was 20 years old, she weighed 176 pounds (80 Kg). She married at this time. Subsequently, she gave birth to 4 babies and gained weight after each delivery. When first seen by Grafe she exhibited enormous adiposity of the trunk, legs and upper arms. During the first month of treatment she lost 30 pounds (14 Kg). Then without change in treatment the loss of weight gradually diminished, and finally, for two weeks there was no loss at all. The weight remained stationary at 341 pounds (155 Kg.). During these two weeks her diet contained 647 calories, and the basal metabolism was 2,000 calories. Grafe calculated that the daily caloric deficit was about 2,000. In addition to the restricted diet her fluid intake was limited to about 500 cc. daily. Under these circumstances the body should have lost 8.5 pounds (4 Kg.) of adipose tissue during these two weeks. Even though the patient received four injections of mersalyl solution and 3 to 8 mg. of thyroxin daily, the volume of urine was small, averaging 500 cc. daily. She continued the treatment at home in a little milder form and lost 13 pounds (6 Kg.) in the next few weeks.

This capacity to resist loss of weight in spite of the most rigorous treatment has given rise to much speculation and confusion. To many physicians it has seemed useless or even cruel to continue to underfeed patients of this type, since they seemed to be doomed to hopeless adiposity.

Wiley and I have seen many examples of this phenomenon. Such paradoxic conduct might arise from some obscure metabolic abnormality that permits conservation in the utilization of energy. In that case, the total heat production would be strikingly less than normal. But no measurement of the twenty-four hour expenditure of energy had been published prior to our reports. Such patients might have been studied in a respiration chamber for one or possibly a few consecutive days. But the restricted activity and short intervals of time imposed by the chamber made that method of doubtful value for this special purpose. We accordingly investigated the feasibility of calculating the dissipation of energy for any desired length of time and without curtailment of activity from the insensible loss of weight, since Benedict and Root [26] had recently shown that there is a quantitative relation between the hourly insensible loss and the basal metabolism.

25. von Noorden, C.: Die Fettsucht, Vienna, Alfred Hölder, 1910.

26. Benedict, F. G., and Root, H. F.: Insensible Perspiration: Its Relation to Human Physiology and Pathology, Arch. Int. Med. **38**:1 (July) 1926.

The method [27] is based on the following considerations: It is well known that evaporation of water from the skin and lungs is one of the mechanisms by which the body rids itself of heat. This portion of the outgoing heat is removed at the rate of 0.58 of a large calory per gram of water vaporized. If an accurate procedure can be devised for the calculation of the weight of the water vapor and if the organism loses a fixed percentage of the heat of its metabolism by vaporization of water under a wide variety of conditions, a method will be at hand for measuring the total heat production day after day.

The direct measurement of water vapor is difficult. However, since the water vapor always accounts for the greater part or all of the insensible loss of weight, the possibility of calculating it from the latter exists.

The insensible loss of weight is easily obtained by substitution in the following equation: I.L. = (initial body weight + ingesta) — (final body weight + urine + stool), where I.L. is insensible loss of weight. And the composition of the insensible loss of weight is accurately defined in the following equation:

$$\text{I.L.} = \text{I.W.} + CO_2 - O_2$$

I.W. represents the weight of the water vapor or insensible water, and CO_2 and O_2 are the weights of the two respiratory gases. It must be understood that insensible water means only that water which leaves the body in the form of vapor. The water vapor is always the largest part of the insensible loss of weight and may be the whole of it, as already noted.

In order to derive the weight of the water vapor from the insensible loss of weight, one must determine the weight of carbon dioxide and oxygen for the period.

To determine whether a fixed percentage of the total heat was removed through vaporization during consecutive twenty-four hour periods by men and women who continued to lead their usual lives, we proceeded as follows (table 11, first group): The subjects were asked to adjust their clothing to avoid conscious discomfort from heat and cold and to forego strenuous exercise, such as handball. The experiments were conducted during the winter months. The subjects spent most of their waking hours in buildings heated to the usual temperature, and each of them was out of doors several times each day for a few minutes at a time. They all slept with the windows of the bedroom open. Two of the subjects were diabetic. The remainder of the group were normal young men and women busily occupied with care of patients or with work in a laboratory. The weight of each person, nude and in the fasting state, was recorded each morning at the same time on

27. Newburgh, L. H.; Johnston, M. W.; Lashmet, F. H., and Sheldon, J. M.: J. Nutrition **13**:203, 1937.

a balance sensitive to 1 Gm. The prescribed diet was prepared and weighed in the special diet kitchen of the hospital. The food used varied from day to day. The weights of the urine and the stool were determined each twenty-four hours.

These experiments were based on the following concepts: A well nourished adult who is following a routine of life and who is fed a fixed diet, the calorific value of which approaches his maintenance requirement, will shortly establish nitrogen balance. In addition, the glycogen store in the liver will come into balance with the carbohydrate of the diet. Thereafter, the person will oxidize carbohydrate in the amount supplied by the diet provided the time interval under consideration is not too brief. It was not expected that this principle would hold for each cycle of twenty-four hours, but that the subject would be in carbohydrate balance if each period lasted one week. Under these circumstances, change in body weight could be attributed to deposition or loss of adipose tissue, provided the observations of any subject were continued for several weeks. When the record was completed, the average daily metabolic mixture would correspond with the diet except that any change in body weight over the whole period would have to be reduced to a daily average and then 90 per cent of it either added to or subtracted from the dietary fat.[28] The calories of the diet thus corrected were taken to be the daily heat production of the subject.

Having arrived at the metabolic mixture, we could calculate the production of carbon dioxide and the absorption of oxygen. Since the insensible loss of weight had been determined for each twenty-four hours, the weight of the insensible water could be derived by means of the equation $I.W. = I.L. - (CO_2 - O_2)$.

When the insensible water is known, the heat removed by it is simply $I.W. \times 0.58$. From this value and the heat production the percentage of heat removed by the vaporization of water was calculated by means of the expression

$$\frac{I.W. \times 0.58}{\text{heat production}}$$

In order to arrive at a diet that would suit our purpose, we fed what experience led us to believe was a maintenance diet, measured the insensible loss of weight daily for at least one week, calculated the gaseous exchange for that diet, derived the insensible water and assumed that 24 per cent of the heat was removed by vaporization. The final diet was then constructed to contain the number of calories indicated by this approximation to the subject's heat production. However, in the case of the 2 diabetic subjects it was not necessary to use a circuitous method to arrive at the materials oxidized, since both had been living

28. Since adipose tissue contains 10 per cent water and dietary fat is expressed in anhydrous terms, 90 per cent of the change in weight is used.

on carefully prescribed, weighed diets for years and had long since come into balance.

Table 11 shows the average percentage of the total heat lost through evaporation of water by each subject.

The first group of 7 adult persons, whose lives were restricted only in the few important ways just noted, showed a striking tendency to rid themselves of the same proportion of the heat of their metabolism by vaporization of water. The average value for the group was 24.4 per cent. The individual values varied from 23.8 to 25.2 per cent.

To obtain greater accuracy when the second group of subjects was studied, the nitrogen exchange was actually determined and the diets were restricted to a few foods the composition of which showed little tendency to vary.

TABLE 11.—*Average Percentage of Total Heat Lost by Evaporation of Water*

Subject No.	Period, Days	Age, Yr.	Sex	Heat Lost by Evaporation of Water, %	Comment
			First Group		
1	72	56	M	23.8	Diabetic patient
2	5	30	M	24.2	Diabetic patient
3	18	28	M	24.2	Chemist
4	44	24	F	24.4	Chemist
5	35	25	M	24.1	Medical student
6	68	23	M	24.7	Graduate student
7	72	24	M	25.2	Graduate student
			Second Group		
8	145	24	M	24.2	Student
9	30	18	M	24.3	Patient in bed
10	30	15	M	24.8	Patient in bed
11	30	18	M	24.8	Patient in bed
12	25	47	M	24.7	Patient in bed

The second, third and fourth subjects were youths aged 15, 18 and 19 who were convalescent from minimal tuberculosis of the lungs but who were still confined to bed. None of them had fever, and they felt well. They lost, respectively, 24.3, 24.8 and 24.8 per cent of the total heat produced by vaporization of water.

The last subject, a man 47 years of age, was in the hospital because of Ménière's disease. He had no attacks during the study. The data obtained on this patient are especially valuable, since he was being underfed and lost 1,787 Gm. in the twenty-five days of observation. The calculation was further complicated by a negative nitrogen balance of 1.36 Gm. daily. Nevertheless, the calculated percentage of heat lost by the vaporization of water was 24.7, even though the metabolic mixture was vastly different from the diet.

The average value for this second group was 24.6 per cent. Hence, the response of these subjects, all but 1 of whom remained in bed, was nearly the same as that of the first group, in which the subjects were leading active lives.

The uniformity of performance of these 12 persons indicates that man displays a strong tendency to rid himself, by vaporization of water, of one fourth of the heat being produced within his body, provided he is comfortable in regard to his environment. These studies also show that this tendency is maintained even when there are large differences in the total amount of heat being removed (2,200 calories to 3,600 calories).

However, since I have thus far been dealing with averages of performances these data give one no information about the extent of the day to day variation in the percentage of heat removed by vaporization of water. In order to obtain information about this question, we made use of a large respiration chamber. It was merely necessary to add to its equipment a balance capable of weighing a human being to 1 Gm.

In addition to obtaining the insensible loss of weight, we determined the production of carbon dioxide, the absorption of oxygen and the urinary excretion of nitrogen. This permitted us to calculate the weight of the water vapor by means of the equation I. W. = I. L. — (CO_2 — O_2) and the heat lost by vaporization of water (I. W × 0.58).

From the carbon dioxide, oxygen and urinary nitrogen we calculated the heat production by the standard procedure.

Next we compared the heat production determined by indirect calorimetry with the value derived from the insensible loss of weight. To make the latter calculation the composition of the metabolic mixture needed to be ascertained. The urinary nitrogen was used as a measure of the protein. It was assumed that the carbohydrate oxidized equaled the carbohydrate of the diet. The fat of the metabolic mixture was calculated by means of an equation suggested by Lavietes.[29] Its derivation follows:

$$\text{I. L.} = \text{I. W.} + CO_2 - O_2$$

$$\text{I. W.} \times 0.58 \times \frac{100}{25}^{30} = \text{Calories}^{31}$$

$$0.58 \times \frac{100}{25} = 2.32$$

$$\text{I. W.} = \frac{\text{Calories}}{2.32}$$

$$\text{Calories} = 4.1\,C + 26.5\,N + 9.3\,F$$

C represents carbohydrate; N, urinary nitrogen, and F, fat.

$$(CO_2 - O_2) = 0.41\,C + 0.84\,N - 0.08\,F$$

$$\text{I. L.} = \frac{4.1\,C + 26.5\,N + 9.3\,F}{2.32} + 0.41\,C + 0.84\,N - 0.08\,F$$

$$\text{I. L.} = 1.77\,C + 11.42\,N + 4.009\,F + 0.41\,C + 0.84\,N - 0.08\,F$$

$$\text{I. L.} = 2.18\,C + 12.26\,N + 3.93\,F$$

$$F. = \text{I. L.} - \frac{(2.18\,C + 12.26\,N)}{3.93}$$

29. Lavietes, P. H.: J. Clin. Investigation **14**:57, 1935.

30. It is assumed that 25 per cent of the heat produced is lost by vaporization of water.

31. "Calories" indicate total heat production for the period.

The heat produced by the oxidation of protein, carbohydrate and fat was determined by multiplying them by their calorific values. The total heat is the sum of these three values.

We performed 39 experiments each lasting twenty-four hours, on 9 young men and women. Each subject was studied two or more times. One of them was in the third trimester of normal pregnancy. The remainder were presumably healthy persons leading active lives.

The variation in the heat lost by vaporization of water during single twenty-four hour periods was from 21.2 to 27.7 per cent. The average value was 25.1 per cent.

When the mean values of the twenty-four hour periods for each of the 9 subjects are examined, it is found that they all fall within the limits of 24.0 and 25.8 per cent. The close agreement of the average performances of the 9 subjects emphasizes the desirability of using the mean of several twenty-four hour periods whenever heat production is calculated from insensible loss of weight.

These experiments have demonstrated that the calculation of heat from insensible loss may be satisfactorily carried out on persons who continue to lead their customary lives provided they do not indulge in strenuous exercise or heavy manual labor. The advantage of measuring heat in this way is that it permits one to obtain a continuous record for as many consecutive days as is desired.

By means of this method we have recorded the heat production of a number of obese persons consecutively for several weeks and sometimes even for months. We have included subjects with various types of obesity described in the literature; that is (1) a person physically normal except for obesity who frankly admitted years of gluttony, (2) a feeble-minded girl with a low basal metabolic rate, (3) a girl with disease of the pituitary and a basal metabolic rate 30 per cent below normal; (4) a middle-aged woman whose weight had reached 295 pounds (134 Kg.) after an operation on the hypophysis eight years earlier; (5) a young woman suffering from so-called "Dercum's disease"; (6) a middle-aged woman 5 feet 2 inches (157 cm.) tall whose weight had reached 420 pounds (191 Kg.) (menopausal obesity). In no case did we find anything unusual about the total metabolism. These patients certainly did not exhibit any capacity to live at a lesser expenditure of calories than normal persons. In fact, just the opposite was true for the patients who were active. The total expenditure was large and indicated that they produced considerably more heat than persons of the same height, age and sex whose weight was normal. Our data are entirely in accord with those of Lauter,[32] who found that an obese subject requires more energy to perform a given piece of work than does a normal control.

32. Lauter, S.: Klin. Wchnschr. **5**:1695, 1926.

Water Balance.—In spite of the large expenditure of energy, we repeatedly encountered periods lasting for a number of days during which the patients failed to lose weight, even though the calories of the diet were far less than the dissipation of heat. A good example of this phenomenon is illustrated by figure 1. The patient was a young woman who weighed 275 pounds (125 Kg.) when she entered the hospital. Her basal metabolism, which was normal, amounted to 2,100 calories per twenty-four hours. Throughout the study she remained in bed. In spite of the inactivity the total twenty-four hourly heat production averaged 2,800 calories.

She received a diet that yielded 1,600 calories daily. She was accordingly compelled to oxidize enough body tissue to yield 1,200

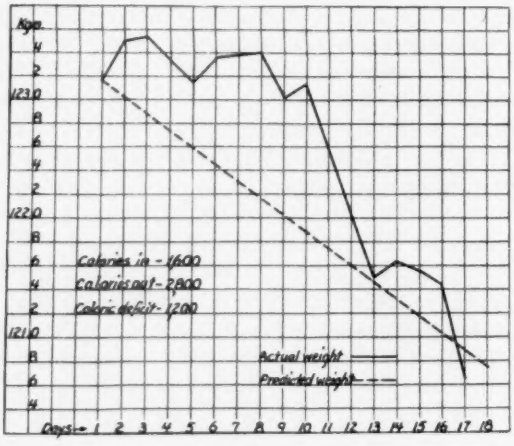
Kgm.
123.0
122.0
121.0
Calories in - 1600
Calories out - 2800
Caloric deficit - 1200
Actual weight
Predicted weight
Days → 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

Fig. 1.—In spite of underfeeding that caused a destruction of body tissue the weight of which amounted to 150 Gm. daily, the patient weighed approximately as much on the tenth day as she did on the first one. Thereafter, she lost weight much more rapidly than could be explained by destruction of body tissue. This biphasic response to underfeeding suggests that the water content of the organism first becomes abnormally large and then recedes to the normal amount.

calories daily. The weight of this tissue was obtained as follows: The patient was placed on the experimental diet one week before the observations began, in order to reduce the carbohydrate stores of the body to the low level after which no more of it would be oxidized to supplement the dietary deficiency. Thereafter, the whole of the caloric deficit was supplied by oxidation of body protein and fat. The amount of body protein destroyed was obtained by subtracting the sum of the urinary and the fecal nitrogen from the nitrogen of the diet and multiplying the difference by 6.25. The number of calories derived from body protein was then subtracted from the total caloric deficit to give the calories

yielded by oxidation of body fat, and the value thus obtained was divided by 9 to give grams of fat. Knowing the grams of pure protein and fat oxidized, we needed to convert these materials to the conditions in which they existed in the body in order to arrive at the total weight of the tissues destroyed. Protein in the living organism is associated with three times its weight of water and fat with one-tenth its weight. When the protein and fat are oxidized, this water is released and excreted. The weight of the tissues destroyed is accordingly the sum of the weights of the hydrated protein and fat. This weight may be subtracted from the weight of the subject at the beginning of the experiment and indicates what he must have weighed on any day if nothing else had intervened to disturb these simple relations. This hypothetic weight is represented in the diagram by the broken line and indicates that about 150 Gm. of body tissue were destroyed daily. The solid line is the actual day to day weight of the patient. In spite of the underfeeding, the patient weighed approximately as much on the morning of the tenth day as she did on the

TABLE 12.—*Water Balance*

Water Available	Water Excreted
In food	In urine
In drink	In stool
By oxidation	Insensibly
From integral combination with tissues (preformed water)	

first. In fact, she actually gained weight the first and the second day. This capacity to resist loss of weight, even though body tissues are certainly being oxidized and the end products excreted, may last for two weeks or longer. But whatever the duration, it always gives way to a subsequent rapid loss of weight greatly in excess of the weight of the tissue destroyed. In the diagram it will be seen that this patient lost as much weight in three days (tenth, eleventh and twelfth) as she was expected to lose in twelve days because of destruction of body tissue.

It seemed to us, a priori, that this phenomenon might be caused by a retention of water subsequently followed by excretion of the excess. Accordingly, we undertook a study of the water balance.[33]

Table 12 shows the various items that go to make up such a balance.

The moisture content of the food, the urine and the stools and the weight of water drunk are determined by standard laboratory methods. The weight of the insensible water is calculated from the insensible loss of weight, as previously described (page 1046). The water of oxidation is that water which arises from the oxidation of the metabolic mixture. The method for calculating the latter from the insensible loss of weight

33. Wiley, F. H., and Newburgh, L. H.: J. Clin. Investigation **10**:723, 1931.

and the excretory nitrogen has already been described. When it is known how much carbohydrate, protein and fat have been metabolized, the water produced by this process is calculated by multiplying by the factors 0.6, 0.4 and 1.07, respectively. The preformed water is that water which forms an integral part of living tissue. When body tissue is oxidized, its water is released and is added to the mobile water of the body, just as if it had entered through the digestive tract. When the data are collected from subjects who are being underfed, the body stores of carbohydrate will be so depleted after a few days that no more of it is available to make up the caloric deficit and thereafter it must be derived entirely from protein and fat. The method of calculating the number of grams of body protein and fat destroyed has already been described (page 1050).

In order to control our work we first studied the water relations in a normal subject while he was being underfed. For the sake of uniformity

TABLE 13.—*Concealment of Destruction of Tissue by Retention of Water*

Day of Experiment	Change in Weight of Subject, Gm.	Weight of Body Tissue Destroyed, Gm.	Water Balance, Gm.
1	+285	90	+369
2	—225	90	—105
3	+ 65	90	+149
4	—125	90	— 41
5	+115	90	+198
Totals	+115	450	+570

he remained in bed except when he took a few steps to the scale or the commode. To minimize error we restricted his diet to milk, sugar and water. He received 63 Gm. of protein, 26 Gm. of fat and 148 Gm. of carbohydrate, yielding 1,078 calories. He produced 1,688 calories daily, derived from 69 Gm. of protein, 91 Gm. of fat and 148 Gm. of carbohydrate (averages for each twenty-four hours). Consequently, he destroyed 6 Gm. of body protein and 65 Gm. of body fat each twenty-four hours. The combined weight of these two substances in their hydrated living state is 95 Gm.

It was soon noticed that this man, even though normal, failed to lose weight smoothly. Like obese persons, for several consecutive days he would lose no weight or he might even gain weight. Then his weight would suddenly decline at a rapid rate far in excess of 95 Gm. daily.

Table 13 shows the water exchange for five consecutive days when the subject weighed 115 Gm. more at the end than he did at the beginning, even though he had destroyed 475 Gm. of body tissue. It is quite clear that the failure of the body weight to keep pace with the loss of tissue is attributable to the retention of water.

Since these events took place in a normal subject, they are deprived of all specificity for obese subjects. The excessive retention of water is seen to be merely a by-product of undernutrition. It in no way indicates that the metabolism of obese persons is abnormal.

In order to leave no doubt that the failure of obese persons to lose weight is explained by retention of water, the following case is cited:

The patient was a girl aged 14 who had always been taller and fatter than the girls of her age. Her progress in school had been slow, and she had repeated many of her grades. She freely admitted overeating and said that she much

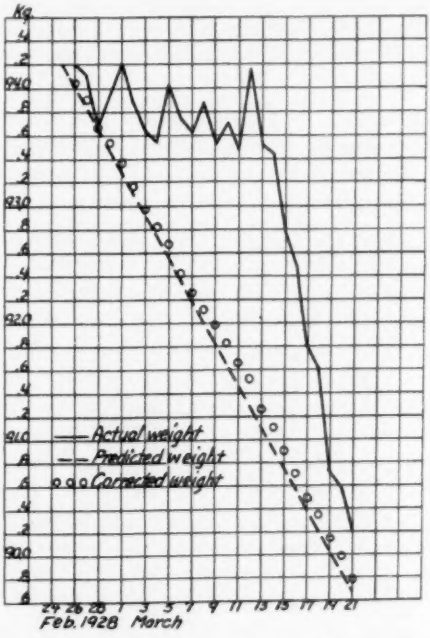

Fig. 2.—A response similar to that portrayed in figure 1. The circles represent the body weight corrected for water retention. The retention of 2,900 grams of water in sixteen days explains the failure to lose weight, since 2,900 grams of body tissue was destroyed during the same period.

preferred sitting quietly without occupation. Menstruation had begun when she was 10 years old and had been regular. She was 6 feet 1 inch (185 cm.) tall and weighed 244 pounds (111 Kg.). There was a luxuriant growth of axillary and pubic hair, and the breasts were large. Her tongue was exceptionally thick and broad. This girl was selected for study because she was obviously an abnormal type. Nevertheless, it will be seen that her failure to lose weight was attributable to retention of water, which is a normal response to underfeeding. The diet consisted of 65 Gm. of protein, 40 Gm. of fat and 74 Gm. of carbohydrate. It contained 914 calories. She produced 2,137 calories daily by metabolizing 73 Gm.

of protein, 172 Gm. of fat and 74 Gm. of carbohydrate. Therefore, the daily destruction of body tissue amounted to 181 Gm. Figure 2 shows her response to the underfeeding for twenty consecutive days. It will be noted that she weighed as much on the sixteenth day as she did at the start. Then a marked diuresis set in without any other change in the conditions of which my associates and I were aware. The diuresis continued for the next nine days of the study, by which time she had lost an amount of weight that approximately equaled the weight of the body tissue destroyed during the twenty-four days. The solid line in figure 2 indicates the actual weight each morning. The broken line states what she would have weighed in response to the destruction of body tissue, if the water balance had not been disturbed. The position of the circles was calculated by subtracting the weight of the extra water in her body from the actual weight. They show that her ability to resist loss of weight for more than two weeks was caused by progressive addition of water, which finally amounted to more than 6 pounds (3 Kg.).

The number of such studies that can be undertaken is limited, but whenever we have carried them through we have been rewarded by the demonstration that the failure of patients to lose weight when they were being underfed was always explained by retention of water.

Increased Absorption of Food.—After it had been generally accepted that obese persons produce more heat than normal controls, the possibility still remained that if the digestion and absorption of food by the obese persons was sufficiently more efficient than that by normal people, the former could succeed in gaining weight without overeating. Nenenschwander-Lemmer [34] has investigated this possibility. He compared the combustible materials in the feces with those in the diet. In a patient 5 feet 4 inches (163 cm.) tall who weighed 231 pounds (105 Kg.) he found 4.96 per cent of the nitrogen and 14.9 per cent of the fat of the diet in the stool. A control of the same height who weighed 125 pounds (57 Kg.) lost 5.49 per cent of the dietary nitrogen and 11.7 per cent of the fat in the stool. The residual calories in the feces of a group of obese persons were 5.47 per twenty-four hours, as compared with 5.41 in persons of normal weight. The utilization of the dietary calories, nitrogen and fat by the obese persons was 87, 84 and 83 per cent respectively. For the controls, the corresponding values were 88, 86 and 89 per cent. Obesity is not caused by an economy of food.

"Lipophilia."—Von Bergmann suggested that adiposity is caused by a hereditary constitutional trait of the adipose cells that enables them to accumulate excessive amounts of fat. He has compared obesity to growth. Just as a youth grows, even though his activity consumes great quantities of food, so some tissues accumulate fat, even though the diet might be insufficient to meet the needs of other organs. Hetenyi [35] carried this idea one step further by postulating that fat once deposited in the depots

34. Nenenschwander-Lemmer, N.: Ztschr. f. d. ges. exper. Med. **99**:395, 1936.

35. Hetenyi, G.: Deutsches Arch. f. klin. Med. **179**:134, 1936.

of an obese person is prevented from leaving them and so cannot be used as fuel. Increased appetite is the natural response.

To support this contention, he compared the levels of the blood fats in obese persons with those of normal persons when the usual food was taken and again after eight days of restricted diet. The data appear in table 14.

I interpret these data as evidence against Hetenyi's hypothesis. Since obese persons have more fat in the blood when food is unrestricted, they must be either storing less or mobilizing more of it than normal persons. The lowering of the blood fat level in obese persons by underfeeding is accepted by Hetenyi as evidence that they have difficulty in releasing fat from the depots in response to the increased call for energy, but it might just as well mean that fat which is being mobilized at a normal rate is being oxidized more rapidly.

Later studies dealt with blood fat curves after feeding 200 cc. of cream. The average increase in the controls amounted to 84 per cent

TABLE 14.—*Blood Levels of Fats*

Condition of Subjects	Usual Diet		Diet Planned to Insure Undernutrition	
	Range, Mg. per 100 Cc.	Average, Mg. per 100 Cc.	Range, Mg. per 100 Cc.	Average, Mg. per 100 Cc.
Obese	544 to 1,117	800	446 to 802	630
Normal	371 to 1,005	591	414 to 997	607

of the fasting values as compared with an increase of only 17 per cent in the obese subjects. The individual responses, however, varied from zero to 157 per cent, and such a wide variation throws considerable doubt on the value of the averages. The lower levels in the obese subjects are offered by Hetenyi as evidence of increased avidity for fat by the depots, but since the greater metabolism of obese persons demands more fuel, why do not the lower levels of fat indicate accelerated oxidation of it?

If it were true that the adipose tissue cells of obese persons resist mobilization of fat in undernutrition, then such persons would not lose weight, or if they did, the loss would represent the destruction of body protein. But the following studies show that obese persons are less likely to go into negative nitrogen balance when underfed than are normal subjects. Jansen [36] placed 15 medical students whose average weight was 62 Kg. on a diet yielding 1,600 calories and 61 Gm. of protein daily for several weeks. Their average loss of nitrogen was 2 Gm. daily. Benedict's [36a] 12 normal subjects receiving 1,534 calories and 51 Gm. of protein lost 65 Gm. of nitrogen from the body in three weeks. On the other

36. Jansen, W. H.: Deutsches Arch. f. klin. Med. **124**:1, 1917.

36a. Benedict, cited by Lusk, G.: Physiol. Rev. **1**:523, 1921.

hand, Keeton and Dickson [37] showed that most obese persons on a diet yielding 1,375 calories and 90 Gm. of protein maintained nitrogen balance, and Strang, McClugage and Evans [38] found that obese persons receiving only 440 calories and about 1 Gm. of protein per kilogram of ideal body weight do not lose body protein.

With these things in mind, my colleague, Malcolm Block, has reinvestigated the response to underfeeding. After determining the total blood lipids during a preliminary period when the diet was unrestricted, he placed 3 normal young women and 3 obese young women on a series of diets. The first diets were arranged to yield approximately 80 per cent of the energy of the basal heat production for twenty-four hours. After seven days, blood lipids were determined again and the diets were

TABLE 15.—*Variation in Total Blood Lipids in Three Normal and Three Obese Young Women on Various Diets*

Diet	Blood Levels of Fats, Mg./100 Cc.	
	Normal Controls	Obese Subjects
Unrestricted	499	700
	523	540
	610	560
80 per cent of basal calories	706	808
	750	575
	710	700
60 per cent of basal calories	846	808
	843	700
	806	850
40 per cent of basal calories	708	910
	605	850
	542	610
20 per cent of basal calories	...	710
		910
		608

reduced to about 60 per cent of the basal heat. Seven days later, samples of blood were again withdrawn and the calories of the diets were reduced to 40 per cent of the twenty-four hourly basal heat production. At the end of this week, samples of blood were obtained and the obese patients were all placed on a diet yielding 450 calories. The blood fat readings are recorded in table 15. An examination of these values indicates that they rose and then fell both in the obese patients and in the controls, and it is not possible to detect any significant difference in the responses of the two groups to underfeeding.

In addition, Block calculated the dissipation of heat from the insensible loss of weight according to the principles described on pages 1044 to 1045.

37. Keeton, R. W., and Dickson, D.: Excretion of Nitrogen by Obese Patients on Diets Low in Calories Containing Varying Amounts of Protein, Arch. Int. Med. **51**:890 (June) 1933.

38. Strang, J. M.; McClugage, H. B., and Evans, F. A.: Am. J. M. Sc. **181**: 336, 1931.

And he estimated the caloric deficit by comparing the energy of the diet with the expenditure of energy. The differences were then converted to weight of body tissue destroyed, on the assumption that it consisted entirely of fat. The results for the 3 obese patients are found in table 16, which also records the daily intake of nitrogen and the urinary nitrogen. It will be seen that each of the patients lost almost exactly the amount of weight that she was expected to lose if the body tissue destroyed to make up the caloric deficit was solely adipose tissue. Furthermore, the comparison between the dietary and the urinary nitrogen shows the patients lost only negligible amounts of body protein.

All of these later studies show that obese persons release fat from the stores as a source of energy as readily as normal persons do. In fact, it seems likely that the obese persons do this more readily, since

TABLE 16.—*Loss of Weight and Daily Dietary Intake and Urinary Output of Nitrogen in Three Obese Subjects*

	Daily Loss of Weight, Gm.		Daily Nitrogen	
No. of Subject	Predicted	Actual	Intake in Diet, Gm.	Output in Urine, Gm.
13	254.6	255.4	13.81	14.34
14	250.7	249.2	13.81	13.35
15	222.8	222.8	13.66	13.75

TABLE 17.—*Respiratory Quotients after a Test Meal*

Hours after meal	1	2	3	4	6	8
Normal subjects	838	810	804	823	812	819
Obese subjects	746	772	752	740	761	795

they usually remain in nitrogen balance when they are underfed, whereas persons of normal weight do not.

The fasting respiratory quotients in obese persons are lower than they are in normal controls. According to the usual interpretation, this means that the former persons are oxidizing more fat. Quotients published by Strang [39] are enlightening. The fasting values obtained from 7 obese patients ranged from 0.698 to 0.830 and averaged 0.757. The controls under similar conditions ranged from 0.770 to 0.848 and averaged 0.783. These same persons were studied again after a test meal consisting of 40 Gm. of protein, 26 Gm. of fat and 52 Gm. of carbohydrate. Quotients were obtained repeatedly after the meal for eight hours and are presented in table 17.

Since both the quotients obtained during fasting and those obtained after the ingestion of food are lower in obese subjects, we have before

39. Strang, J.: Am. J. M. Sc. **182**:69, 1931.

us classic evidence that such persons are metabolizing more fat than the normal controls. They cannot at the same time be storing more fat or withholding more of it in the depots.

Summary.—These many painstaking investigations of the metabolism of obese persons have failed to disclose any abnormal process that accounts for the accumulation of the fat. On the contrary, they have demonstrated that obese persons produce more heat in the basal state, that they expend more energy to perform a measured amount of work and that their total heat production is greater than that of normal persons of similar age, height and sex under the same circumstances. Since they are unable to absorb more energy from their food, they must eat more than normal people simply to avoid loss of weight.

ENDOCRINE DISORDERS AND OBESITY

In an age when the vast influence of the internal secretions on bodily states is being emphasized by a host of workers, it is but natural that various endocrine glands have been accused of causing obesity.

Thyroid.—Those writers who believe that the endocrine etiologic basis of obesity has been established have expressed opinions that hypothyroidism is a frequent cause of adiposity. They based the diagnosis on a basal metabolic rate of — 10 to 25 per cent, with or without feelings of sluggishness, coldness and ease of fatigue. But these subjective complaints are so vague and commonplace that they are of almost negligible diagnostic import.

Before interpreting a low basal metabolic rate as a pathognomonic sign of hypothyroidism it is essential to recall some of the details of the test. In the first place, the apparatus records solely the amount of oxygen absorbed in a unit of time by the patient. To compare this value with a standard, the surface area of the patient must be calculated from his height and weight in order to obtain his absorption of oxygen per square meter of his body surface. This value is then compared with the average absorption per square meter of presumably normal persons of the same sex and age. These control subjects are assumed to have been completely relaxed during the test. But if some of them were not because they were a little apprehensive or uncomfortable, then the standards in general use are too high. And those best qualified to judge do, in fact, state that the standards are 5 per cent or even 10 per cent too high. Hence, a patient whose basal metabolic rate is reported as — 10 per cent may be merely one who is completely relaxed or who has fallen asleep. (Sleep lowers the rate 10 to 15 per cent.) Most of the investigators in this field have rates 10 per cent or more below the alleged normal for them, and they are probably merely demonstrating that their familiarity with the technic permits a degree of relaxation that was assumed to have occurred, but may not have, in the controls.

Some persons who are entirely at home in the metabolic laboratory have rates year after year that are 20 or even 25 per cent too low, according to the standards, and still they exhibit the attributes of health and have not become obese or myxedematous.

The custom of paraphrasing a low metabolic rate by the term "hypothyroidism" is not justifiable and certainly is misleading. If a physician wants to give a clinical interpretation to the phenomenon of lessened rate of absorption of oxygen, he can speak of hypometabolism without saying more than the facts justify. He will then be in the same position as when he deals with fever or leukocytosis. He will know that these abnormalities mean little by themselves but that when they are associated with certain other signs of disease, and only then, he is justified in making a diagnosis. When hypometabolism is associated with the classic features of myxedema, it is of course proper to attribute the clinical picture to hypothyroidism, but there exists no sound basis for believing that hypometabolism in the absence of a pale puffy face with stupid expression, hoarse voice, scanty coarse hair, water-logged tissues, anemia and general sluggishness is a sign of early or preclinical myxedema, for transition from a state in which the basal metabolic rate is as much as 30 per cent below standard, even if accompanied by mental and physical inadequacy, into classic myxedema has not been reported. Nor do the improvement in intellectual capacity and in the texture of hair, nails and skin; the relief of constipation, and the correction of menstrual irregularity obtained by administration of desiccated thyroid establish that the symptoms were caused by hypothyroidism. It must be remembered that the thyroid hormone stimulates the metabolism of all the cells. Their augmented activity may well correct symptoms that were caused by sluggish function for any reason.[40]

It seems much more likely that the fatigue of which many obese persons complain may be an actual indication that their muscles and other

40. The material dealing with the interpretation of basal metabolic rate was submitted to the scrutiny of Dr. J. H. Means, who for many years has directed the Thyroid Clinic of the Massachusetts General Hospital. He replied, "I agree with all you say and would like to add my conviction that the functional activity of the thyroid gland can be gaged unequivocally by determining blood levels of iodine. Riggs and Mann, Curtis and others have devised methods which permit the accurate measurement of the concentration of organic iodine in the blood, that is to say the fraction of the iodine which constitutes an integral part of the thyroid hormone, and it has been shown by these investigators that whereas values in normal persons are 4 to 8 micrograms per hundred cubic centimeters, in patients with myxedema they are only 1 to 4 micrograms per hundred cubic centimeters.

"Thus when it is desired to establish a relation between hypothyroidism and obesity, it would be well for investigators to publish readings of the organic iodine in the blood of suitable patients as well as basal metabolic rates."

organs are becoming exhausted by overwork. Is this not the true explanation of the rapid improvement that comes with rest in bed and sharply restricted diets?

Finally, it must be emphasized that even low basal metabolic rates need not cause obesity. The organism, at least in the ideal state, obtains the amount of food that will replenish its losses. When the outgo lessens, appetite diminishes proportionately. This relation between expenditure and intake is shown beautifully by some recent experiments carried out by MacKay and Sherrill.[41] They introduced their data on rats with the remark,

> Although it is well known that patients with myxedema are not obese as a rule, the idea persists in the clinical literature that hypothyroidism may be a cause of obesity.

In order to observe the effect of complete absence of the thyroid hormone, the gland was removed from a group of rats 170 days old. A similar group was selected for control, and all the animals were offered the same diet ad libitum. Three hundred and ten days later the controls weighed 457 Gm. and had gained 193 Gm. But the thyroidectomized animals gained only 178 Gm. Still more interesting was the difference in the fat content of the two groups. The bodies of the controls contained 31.1 per cent of fat, whereas only 6.4 per cent of fat remained in the bodies of the rats deprived of their thyroid glands. Since the latter animals did not appear to be less plump than their controls, it was assumed that edema fluid had been substituted for adipose tissue.

Even more enlightening is the recent statistical investigation of this general question by Plummer[42] on 200 patients suffering from various grades of myxedema. Sixty-one and five-tenths per cent were overweight. In 8.5 per cent the weight was more than 50 pounds (23 Kg.) above normal, but in 5.5 per cent it was more than 30 pounds (14 Kg.) below normal. The greatest excess weight corresponded to the least depression of metabolism, and those patients whose basal metabolic rates were lowest weighed the least. Thus those whose rates were not less than —28 per cent weighed 11.5 per cent too much, whereas those whose rates were less than —38 per cent weighed 14.7 per cent too little. The average excess weight for the whole group was 10.1 pounds (4.5 Kg.). During the first days of medication with thyroid there was an abrupt loss of weight that averaged 13 pounds (6 Kg.). This was brought about by elimination of fluid, since most of the patients were definitely edematous prior to treatment. Now the group weight had become 2.9 pounds (1.3 Kg.) less than normal. The excessive weight so commonly attributed to superabundance of adipose tissue is more

41. MacKay, E. M., and Sherrill, J. W.: Endocrinology **28**:518, 1941.
42. Plummer, W. A.: Tr. Am. A. Study Goiter, 1940, p. 88.

properly interpreted as evidence of abnormal accumulation of water. In fact, judging by MacKay's rats, athyrea causes wasting of adipose tissue.

Pituitary.—Fröhlich's [43] report in 1901 of a case of tumor of the hypophysis without acromegaly seems to have originated in belief that hypopituitarism is a common cause of obesity, especially among children. He described a boy 14 years old who weighed 54 Kg. For two years he had been suffering from attacks of vomiting and headache. The left eye had become blind. The mother stated that the boy's weight had begun to increase rapidly a few months earlier. The examination revealed atrophy of the left optic nerve and right temporal hemianopsia, evenly distributed adiposity, enlargement of breasts, absence of axillary hair, pubic region suggestive of feminine type and dryness and local thickenings of skin. Fröhlich concluded that the rapidly developing obesity should be accepted as a sign of hypophysial tumor. The author cited a number of cases of similar condition proved at autopsy, but he also pointed out that poor nutrition was not uncommon in other cases of proved hypophysial tumor. Certainly there is nothing in this original report to indicate that the obesity was anything more than incidental, especially since the author himself stated that emaciation is commonly encountered in cases of hypophysial tumor.

Because of his preeminence as a neurologic surgeon the conviction arrived at by Cushing based on many careful clinical and experimental studies was accepted for a time as established fact. In 1912 he [44] wrote:

> A number of animals [dogs] in our first series, having recovered after partial extirpation of the hypophysis, were observed to grow very fat. In the second series similar results were noted. The fat proved to be widely distributed. It was not tender and no lipomata were observed.

Speaking of the clinical features of hypopituitarism in human beings, he stated:

> The acquisition of an excessive subcutaneous deposit of fat is one of the notable features and often so dominates the picture as to lead to its inclusion under the following titles: adiposis dolorosa (Dercum's Disease), adiposis universalis, dystrophia adiposo-genitalis (Fröhlich's Disease), adiposis cerebralis. Undoubtedly a number of cases called adiposis dolorosa must be due to hypophyseal deficiency. A pituitary glioma was found by Burr in 1900 in a typical case. McCarthy found an adenocarcinoma of the pituitary in one of Dercum's cases. Lyon found an aneurism pressing upon the hypophysis.

However, in other supposed examples of Dercum's disease no changes were found. Cushing saw a woman whom he believed to be suffering from Dercum's disease. She weighed over 300 pounds (136 Kg.), but he could not locate any lesion in the pituitary.

43. Fröhlich, A.: Wien. klin. Wchnschr. **15**:883, 1901.

44. Cushing, H.: The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912.

Somewhat later Cushing delineated the syndrome that goes by his name and attributed it to adenoma of the basophilic cells in the anterior hypophysis. Patients with this syndrome often exhibit a disproportion between the trunk and the extremities because of the increased girth of the chest and abdomen. Cushing attributed the enlargement of the trunk to excessive deposits of fat and reasoned that a localized adiposity could not arise from overeating but must be a direct outcome of the disease of the pituitary.

Cushing is but one of many writers who have suggested or even asserted that the obesity associated with dyspituitarism results from some unusual metabolic disturbance which in a mysterious way causes an increased synthesis and deposition of fat. Kraus has even reasoned that

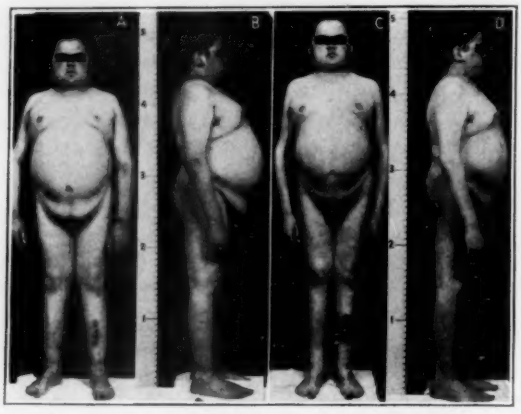

Fig. 3.—A patient with Cushing's syndrome. *A* and *B*, note the appearance of extreme obesity with an excess weight of only 50 pounds (23 Kg.). *C* and *D*, the same patient after reduction of the weight to normal. Nevertheless, the semblance of obesity persists.

a disturbance in fat metabolism is the fundamental abnormality in Cushing's disease.

Three associates and I [45] have recently had the opportunity of studying a case of Cushing's syndrome in which subsequent postmortem examination disclosed a basophilic adenoma of the pituitary, but we arrived at a different explanation of the abnormal bodily shape. The data that deal with the patient's configuration are reproduced here

45. Freyberg, R. H.; Barker, P. S.; Newburgh, L. H., and Coller, F. A.: Pituitary Basophilism (Cushing's Syndrome): Report of Verified Case with Discussion of Differential Diagnosis and Treatment, Arch. Int. Med. **58**:187 (Aug.) 1936. Freyberg, R. H., and Newburgh, L. H.: Obesity and Energy Exchange in Verified Case of Pituitary Basophilism, ibid. **58**:229 (Aug.) 1936.

because they show that the protuberance of the thorax and the abdomen was caused by a condition totally unrelated to adiposity.

As a child, the patient enjoyed exceptionally good health. When he was 12 years old he began to gain weight rapidly. At the age of 19, when he entered the hospital, he weighed 185 pounds (84 Kg.) and was 5 feet 2 inches (157 cm.) tall. His appearance at that time is protrayed in figure 3.

As part of the study he was placed on a diet the composition of which was the same for fifty-four days. It supplied 890 calories daily.

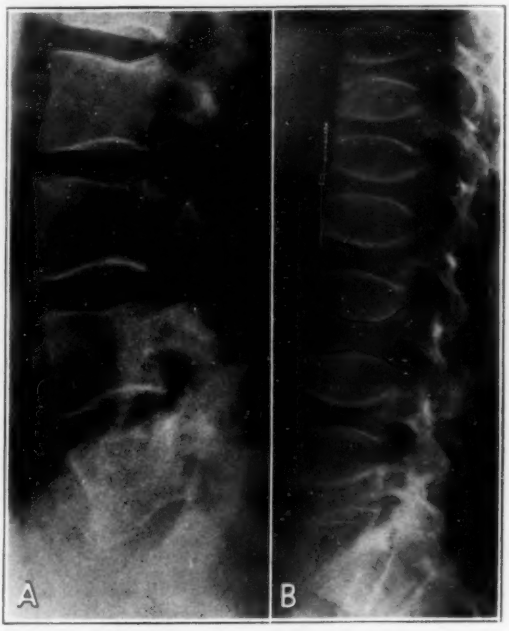

Fig. 4.—Lateral roentgenograms of spinal columns. *A*, normal control. *B*, the patient in figure 3. Note how decalcification has caused thinning of vetebral bodies and shortening of the spine (fish vertebrae).

The heat production was calculated from the insensible loss of weight and the urinary nitrogen, as described on page 1048. From these data we predicted that he should have lost 8,376 Gm. He did lose 8,398 Gm. This remarkably good argreement indicated that the energy exchange was entirely normal and was strong evidence that he had become obese because the inflow of energy had exceeded the outflow.

The loss of 50 pounds (23 Kg.) and the return to normal weight altered little the appearance of the unusually prominent chest and

abdomen and did not reduce their size any more than that of the extremities. Hence, the disproportionate enlargement of the trunk could not have been due to obesity. A lateral roentgenogram did, however, reveal the actual reason for the deformity. The decalcification of the skeleton, a common finding in Cushing's syndrome, had so thinned the vertebrae that the spine had collapsed, with resulting kyphosis and shortening to such an extent that the ribs had been elevated anteriorly until they were horizontal. This had swung the manubrium

Fig. 5.—Lateral roentgenogram of the thorax of the patient in figures 3 and 4 *B*. The ribs are horizontal because of shortening of spine. This has forced the lower end of the sternum upward and forward, carrying the anterior half of the diaphragm with it. The marked increase in the anteroposterior dimension of the thorax is evidenced by the horizontal position of the heart.

forward and upward. The anterior abdominal wall necessarily also moved forward. A perfect explanation for the enlargement of the trunk had been found without involving obesity. In fact, scrutiny of the cases brought together by Cushing and more recently by Freyberg reveals that obesity was not prevalent. Rather were the patients disfigured by protruding abdomens, barrel chests, short necks, kyphosis and wasted musculature.

It is of further interest that the penis and scrotum of our patient were almost invisible on admission. This appearance is held to be characteristic of Fröhlich's disease (adiposogenital dystrophy). However, when the weight had been reduced, the penis and testes had assumed the usual appearance.

Two recent publications present further evidence that the abnormal bodily configuration in patients suffering from Cushing's syndrome is

Fig. 6 (Willson, Power and Kepler [46]).—Note the bulging abdomen in spite of emaciation. The spinal deformity in this patient caused pronounced lordosis.

not dependent on adiposity. Willson, Power and Kepler [46] discussed a patient who had lost 25 pounds (11 Kg.) during the four weeks before he entered the clinic, at which time he weighed 118 pounds (54 Kg.). The accompanying photograph leaves no doubt about the emaciated state of the patient. But, nevertheless, the abdomen bulges to a striking degree, and the authors spoke of the characteristic plethoric

46. Willson, D. M.; Power, M. H., and Kepler, E. J.: J. Clin. Investigation **19**:701, 1940.

moon face. The origin of these abnormalities is explained satisfactorily by Albright without attributing them to increases in adipose tissue, as will appear shortly. Albright, Parson and Bloomberg [47] studied 3 women with Cushing's syndrome and emphasized the apparent girdle obesity, "which is more the result of a relaxed abdominal wall and crushed vertebrae [decalcification] than of actual fat." Two of the women each weighed 118 pounds (54 Kg.). Certainly they were not

Fig. 7 (Albright, Parson and Bloomberg [47]).—Apparent girdle obesity caused by muscular atrophy.

obese. Nevertheless, the photograph of one of them does give the appearance of the so-called "girdle obesity." Albright and associates pointed out that there is a striking destruction of body protein in these patients, as evidenced by the continued negative nitrogen balance. Under such circumstances, a great wastage of the musculature takes place and the abdominal muscles are no longer able to resist the intra-abdominal pressure.

47. Albright, F.; Parson, W., and Bloomberg, E.: J. Clin. Endocrinol. **1**: 375, 1941.

During the early years of this century, other investigators in addition to Cushing endeavored to elucidate the functions of the pituitary by observing the effects of its removal. Opinion was divided. Like Cushing, several other investigators expressed the belief that they had demonstrated that hypophysectomy caused obesity. But Bailey and Bremer, as well as Camus and Roussy, were in doubt, since they found that injury of the brain adjacent to the pituitary was also capable of producing excessive depositions of fat. Finally, it was conclusively demonstrated by Philip Smith,[48] working with rats, that the removal of the hypophysis from these animals did not cause obesity. However, when the hypothalamus was injured by injection of chromic acid, obesity developed regularly after the operation. Smith explained the occurrence of obesity in the dog and its absence in the rat by pointing out that the hypophysis in the dog is separated from the brain by only a gauzelike membrane which invariably ruptures during the operation, whereas in the rat the membrane is firm and resistant. In his operations on the rat, the membrane remained intact and hypophysectomy invariably produced loss of weight, atrophy of the thyroid, the adrenal cortex and the sex organs, and cachexia.

Knowledge is now sufficiently advanced to permit the recognition of hypopituitarism when sufficient skill and effort are devoted to the clinical study. The disturbances sought for are based on the recognition that the anterior lobe of the pituitary secretes hormones which control the activity of the thyroid, the adrenal cortex and the gonads, as well as the utilization of dextrose. Its ablation in young animals causes cessation of growth in addition to atrophy of the glands just mentioned. In the adult human being the disease described by Simmond and shown by him to be due to destruction of the anterior lobe of the pituitary presents the counterpart of the condition produced by experimental ablation of the hypophysis. Here also, the most prominent features are emaciation and atrophy of the thyroid, the adrenal cortex and the gonads. Even diminished function is also recognizable, since it produces clinical pictures that suggest myxedema, Addison's disease, various signs of lessened activity of the reproductive glands and hypoglycemic episodes, present in various combinations from patient to patient. Obesity is not a feature of any of these states.

It is no longer justifiable ever to attribute obesity to hypopituitarism until its presence has been firmly established by carrying out the type of study already indicated. If occasionally patients should be discovered in whom obesity and hypopituitarism are associated, it still needs to be

48. Smith, P. E.: Relations of the Activity of the Pituitary and Thyroid Glands, in Harvey Lectures, 1929-1930, Baltimore, Williams & Wilkins Company, 1930.

established that the former was caused by the latter. To do so, the first step would be to show a high degree of correlation between the two conditions. The clinical studies in this regard, to be discussed shortly, lead to just the opposite conclusion.

Hypothalamus.—Ranson and his associates [49] placed lesions in the hypothalamus in nearly 50 monkeys, 300 cats and many guinea pigs without obtaining obesity. Subsequently, they injected chromic acid into the hypophysis in rats by a technic that they hoped would avoid the hypothalamus. Only 3 of 50 rats became fat. Hypothalamic lesions of considerable extent were found in these 3 animals. The hypophysis showed all degrees of destruction in the 47 rats in which obesity did not develop. In another series they used the Horsley-Clarke instrument, which permits accurate localization, to place lesions in the hypothalamus in 12 rats. All became markedly obese. Subsequent examination revealed large lesions in the hypothalamic area. The hypophysis was intact. These experiments have excluded lesions of the pituitary as a cause of obesity in lower animals, and they cast formidable doubt on the proposition that obesity in human beings is ever originated by destructive disease of the hypophysis. Nevertheless, they do not preclude the possibility that hyperfunction of the pituitary is capable of inducing adiposity. However, in such typical examples of hyperfunction of the pituitary tissue as acromegaly and gigantism the excessive weight is not due to overdevelopment of adipose tissue, but rather to the overdevelopment of the skeleton and organs. And it has just been pointed out that in Cushing's syndrome, another type of hyperpituitarism, obesity is not common and certainly is not a cardinal feature of the disease.

The animal experiments seem to have demonstrated that lesions of the brain in the hypothalamic area are regularly followed by development of obesity in rats. But perhaps of more importance is the failure to produce obesity in the other mammalian species in which the hypothalamus was injured. The negative results obtained by Ranson and associates on a large number of monkeys casts a good deal of doubt on the proposition that hypothalamic lesions in human beings are the actual cause of the obesity that is sometimes seen in patients afflicted with disease of that portion of the brain.

Some light on this difficult question has been shed by Eaves and Croll [50] and also by Greene.[51] The first-named authors concerned themselves with the occurrence of obesity in patients with epidemic

49. Ranson, S. W.; Fisher, C., and Ingram, W. R.: Endocrinology **23**:175, 1938. Hetherington, A. W., and Ranson, S. W.: Proc. Soc. Exper. Biol. & Med. **41**:465, 1939.

50. Eaves, E. C., and Croll, M. M.: Brain **53**:56, 1930.

51. Greene, J. A.: Ann. Int. Med. **12**:1787, 1939.

encephalitis. They report that Grollman noted obesity in 15 per cent of 89 patients, mostly children, and that 8 per cent of Duncan's 83 patients were obese. Hall and Stern recorded a number of obese patients in their monographs on encephalitis. On the other hand, many patients were wasted. The authors examined the brain in 10 patients who died. Two were obese; 4 were cachectic, and the remaining 4 did not show any important change in weight. In summary they stated:

> There is frequently some change in the pituitary but the part played by it in the production of obesity remains obscure. The hypothalamic region was more severely affected than any other region of the brain except the substantia nigra. Severe lesions of the hypothalamus do not give rise to obesity but less intense ones may.

Statistical Inquiry.—Greene endeavored to discover the cause of obesity in 350 cases. He found that inactivity had occurred at the time of gain in weight in 68 per cent of the cases and that a long illness had necessitated the inactivity in 64 per cent of them. He also studied the records of 87 cases of chronic encephalitis, 18 cases of myxedema and 18 cases of tumor of the pituitary. Table 18 shows the results.

Normal weight was the commonest condition in encephalitis, and loss of weight occurred five times as often as gain. When obesity did exist, it had usually preceded the disease. These statistics throw grave doubt on the role of hypothalamic lesions as a specific etiologic factor in obesity in human beings.

Overweight was more frequent in the group of tumors of the pituitary, but the adiposity usually antedated the disease, and loss of weight occurred oftener than gain of it. Again there is nothing in any case to indicate that the nutritional state bore any specific relation to the disease of the pituitary. Even in myxedema obesity was noted in only half the cases, and it had usually existed before the onset of the disease. Weight was lost in more cases than it was was gained.

The inactivity enforced by these chronic illnesses associated with good appetite seemed to be the actual cause of the adiposity when it did occur.

Juvenile Obesity.—Many obese children are assumed to be suffering from hypopituitarism (Frölich's syndrome) or hypothyroidism, even though one searches in vain for sufficient facts to support the contention. Bruch's [51a] dispassionate study of these questions is therefore welcome. Her material consisted of 102 patients, equally divided among girls and boys, 2 to 13 years old, in whom obesity was the outstanding clinical condition. Weight at birth was normal; normal development

51a. Bruch, H.: Obesity in Childhood: I. Physical Growth and Development in Obese Children, Am. J. Dis. Child. **58**:457 (Sept.) 1939.

was the rule, and puberty was attained at normal age or earlier. Obese children are taller than normal ones, and skeletal growth, as determined by roentgen rays, is accelerated. Normal girls who menstruate early are taller and heavier than those in whom the onset is later. Bruch concluded:

> The condition of the obese children manifests an exaggeration of a developmental trend observed in normal children; the difference is only quantitative. . . .

She found that the oxygen consumption of an obese child is greater than that of a normal child of the same age and height. The serum cholesterol, which is increased in myxedema, was normal in 72 obese children. Bruch was satisfied that

> . . . the course of growth and development of obese children . . . cannot be brought into agreement with the well defined picture of hypothyroidism [or] . . . hypopituitarism. . . . It is not reasonable to explain accelerated development as resulting from hypofunction of glands the growth-promoting qualities of which are firmly established. . . .

TABLE 18.—*Weight in Relation to Certain Diseases*

	Chronic Encephalitis	Myxedema	Tumor of the Pituitary
Normal weight	52	11	7
Underweight	19	1	4
Overweight	16	6	7
Relation of Obesity to Onset			
Antedated	16	4	5
Postdated	5	3	3
Disappeared with	5	1	1
Change in Weight after Onset			
No change	16	8	6
Gain	6	6	5
Loss	33	5	7

Nevertheless, the treatment of choice and often the only therapy of the children referred to the obesity clinic continues to be administration of endocrine products, according to Bruch. When pituitary preparations have been recommended, the physician has done so because he has made a diagnosis of adiposogenital dystrophy, basing it on the presence of adiposity coupled with retarded development of the genitalia. But recent studies have made it clear that genital infantilism is far less common than is widely believed. In this connection, Bigler, Hardy and Scott [52] pointed out that the incidence of undescended testicle in the United States Army is 0.3 per cent, whereas at the Hospital for Ruptured and Crippled, New York, incomplete descent was diagnosed

52. Bigler, J. A.; Hardy, L. M., and Scott, H. V.: Gonadotropic Principle in Treatment of Cryptorchidism: Review of Literature, Am. J. Dis. Child. **55**:273 (Jan.) 1938.

in 3.0 per cent of 18,000 children. This means that in 9 of every 10 children in whom the diagnosis is made, the testicles will subsequently descend spontaneously. Browne [53] called attention to a series of misconceptions which lead to incorrect diagnoses. He states that any position from which the testes will reach the scrotum is normal and that the belief that a testicle which can be felt in the region of the inguinal canal is in that canal is a common mistake. Gonadotropic substances will not bring down a testis that would not have descended without such treatment. Its only power is to hasten descent. Spence and Scowen [54] confirmed Browne's findings. Accordingly, the descent of a testicle in a fat boy after treatment with gonadotropic substances should not be accepted as evidence that he was suffering from hypopituitarism. Bruch stated that in none of her patients who had been made miserable and unhappy by a diagnosis of sexual maldevelopment was this diagnosis justified.

In a recent publication Bruch [55] reported the histories of 2 children in order to emphasize that the diagnosis of an endocrine cause of juvenile obesity is not supported by the known facts. But even more impressive is her convincing argument that serious harm may be done to children who receive glandular therapy unnecessarily.

When the first patient was 5½ months old, he had been examined at a pediatric clinic. No abnormalities other than poor development of the genitals had been found. When the child was 15 months old, a physician in the urologic clinic had been unable to feel either testicle, and treatment with chorionic gonadotropin (follutein) was begun. The child had continued to receive courses of this material subcutaneously until he was 6 years old. When he became a patient of the Pediatric Obesity Clinic, a division of Vanderbilt Clinic, New York, it was noted that the genitalia appeared small. Their true size however was masked by an accumulation of suprapubic fat. When this was pushed back, it was seen that the penis and scrotum were well formed. His weight had been normal when the glandular treatment was started, and it was not realized that he was gaining weight too rapidly until he was 6 years old, when he weighed 45 per cent in excess of the normal. At this time a diagnosis of "adiposogenital dystrophy" was made because of the marked accumulation of fat in the abdomen, suprapubic region and thighs and the round face and sluggish expression, together with the apparently infantile genitalia. Bruch pointed out that the development of the so-called "pituitary" type of obesity in a patient being treated intensively with gonadotropic substance is substantial evidence against the correctness of such a diagnosis.

It was now learned that the patient, who was an only child, had experienced a local swelling with pain and a general reaction consisting of rise in temperature to 102 F. accompanied by nausea after each injection. Nevertheless, he had been given three injections weekly for protracted periods. Shortly after the treatment was begun, he had become apprehensive and listless. He never was able to dress

53. Browne, D.: Brit. M. J. **2**:168, 1938.
54. Spence, A. W., and Scowen, E. F.: Lancet **2**:983, 1938.
55. Bruch, H. J.: J. Pediat. **18**:36, 1941.

himself and did not care to play. On the other hand, he always enjoyed his food and ate everything his mother gave him. In retrospect, she realized that she had overfed him to compensate for his illness.

After the first visit to the Obesity Clinic he was lost track of for a year. The explanation was then forthcoming. Because of prolonged illness both of mother and of father the patient had been shifted from one relative to another. Finally, a crippled woman, who could do little for him, was put in charge of him. At the end of this year he was a changed child. He dressed and bathed without aid, did not object to being left alone, played on the street and defended himself. In spite of growing 2 inches (5 cm.) he had lost 5 pounds (2.5 Kg.).

In retrospect, it is seen that the persistency of subcutaneous medication, even though it caused unpleasant reactions, naturally led the mother to surmise that her only child was seriously abnormal. The patient's timidity and listlessness were further evidence that he was suffering from a chronic illness. She responded by attempting to compensate for his disability by protecting him in every way and by giving him the satisfaction obtainable from large and varied feedings.

The second patient, a girl, had been brought to the Pediatric Department when she was 5 years and 2 months old for treatment of asthma, from which she had suffered for six months. Her weight was normal. After one year's treatment she had had no further attacks. At that time, when her weight was still normal, moderate enlargement of the thyroid had been noted. Accordingly, she had been followed in the Thyroid Clinic for the next five years. There it was recorded that the gland was nodular and firm, but that there were no manifestations of hypothyroidism. The basal metabolic rate was —30 per cent, according to the surface area standard. One week later it was —13 per cent. Calculation of the rate on the basis of height and weight standards gave values of +5 per cent and —2 per cent, respectively. For prophylactic purposes she had been given minute amounts of thyroid and syrup of hydriodic acid U. S. P. for the next two years. During this period she had gained weight rapidly and had become markedly obese. When she was 11 years of age, the thyroid gland was considered to be normal. The basal metabolic rate at this time was —19 per cent according to surface area standard, ± 0 according to height standard and —8 per cent when referred to weight.

When seen for the first time in the Obesity Clinic she was 10½ years old and 40 per cent overweight.

The patient, an only child, had never been allowed to go out in cold or wet weather, and association with other children had been discouraged by the parents with the hope of avoiding asthmatic attacks. Up to the age of 12 she had not been allowed to take a bath alone and was still being sent to the toilet. Even though the last attack of asthma occurred when she was 6, the parents were afraid to relax the precautions devised to protect their child.

The obesity was explained by the parents and the patient as due to the "lazy gland," even though the family had been reassured repeatedly that the thyroid was normal. When a reduction diet was suggested, the mother expressed fear that it would be harmful to a child with a "lazy gland," and the patient was openly antagonistic to any treatment.

In this case as in the previous one the exaggerated anxiety and misinterpretation of the medical situation resulted in parental conduct that deprived the children of most of their normal outlets. They became self centered and considered themselves deserving objects of pity and special consideration. Under such circumstances the satisfactions derived from eating were about the only pleasures still permitted the children. It would have been strange indeed if they had not made the most of them.

My associates and I have been especially interested in the obesity of young adults that had its onset years earlier in association with an illness. Careful questioning is usually rewarded by the discovery that the mother had been instructed to prevent all physical activity on the part of her child, who had just passed through an illness which was thought to have caused heart disease. Even though activity is cautiously increased months later, the young patient continues to be trained to avoid exercise and to guard against heart strain. The mother, not realizing that the needs for food are greatly reduced in these circumstances and still under the sway of the time-honored belief that recovery will be enhanced by full feeding, spares no effort to tempt the child to eat. The young patient, suffering from self pity and egoism, accepts the food, even though he has no inherent desire for it. As time passes, conditioned reflexes become firmly developed, and the feeling of satiety does not occur until the child has overeaten in the physiologic sense.

HEREDITY

The interesting observations published by Danforth [56] proved that in at least one mammalian species there exists a gene that causes its possessor to become obese with great regularity. Yellow male mice were mated to females of various colors. Some of the descendants were yellow, others were not. Litter mates were kept in the same cage and had access to the same food. After sexual maturity had been attained, the yellow mice began to gain weight more rapidly. This was especially true for the yellow females, many of which reached a weight twice that of their mates. The excess weight was mainly due to a great and widely distributed increase in adipose tissue. Our own studies, still in a preliminary state, of this hereditary obesity of yellow mice permit the statement that the mice which become obese eat more than the others. Evidently one is dealing with a hereditary bulimia.

Before considering whether a similar gene is transmitted by human beings, it will be well to give some thought to the configuration of the body. No one questions the inheritance of bodily shape or build. Everyone is familiar with the characteristic lines of purebred dogs. One has merely to recall the contrasts between the slender, graceful, agile grey-

56. Danforth, C. H.: J. Heredity **18**:153, 1927.

hound and the thick-set, ponderous English bulldog. But even though the bulldog is robust and powerful, he is not obese. However, he may be pampered into overeating and become so.

Similarly, the human being who has inherited a sthenic build is not predestined to become obese. Pains must be taken to explain to him that the two qualities are not linked—that while shape is inherited, obesity is an acquired characteristic.

Adipose tissue is much more abundant in some parts of the body than in others, and women normally possess more fat than men. Furthermore, there is commonly a large accumulation of fat around the hips and loins of women of normal weight. And since the pelvis of a woman is flatter than that of a man, she starts with two handicaps when she becomes obese. The so-called "girdle" obesity merely accentuates a normal type of feminine configuration. While it may well be true that the deposition of the excessive fat in the central regions of some women is an inherited characteristic, it is also true that there would have been no extra fat to deposit in those regions had the intake of food not been overabundant.

The prevalence of obesity in some families need not be accepted as an inherited and therefore an unavoidable trait. A more realistic explanation is the continuation of the familial tradition of the groaning board and the savory dish.

The question of whether human obesity is an inherited characteristic has been investigated extensively. Such studies are based on the proposition that identical twins are genetically identical throughout and that differences in the individuals of such a pair are due to environmental influences. Accordingly, differences in body weight are caused by environmental influences. Both Verschuer [57] and Newman and associates [58] found that weight varied more than any of the other anthropologic measurements. In fact, the average variation in weight was always twice, and mostly three times, as great as that of any of the other variables. This emphasizes the important influence of environment on weight.

Furthermore, Verschuer compared the variations among identical twins living under similar conditions with those among twins living under dissimilar conditions. Differences in weight were two and a half times as great when environment was dissimiliar. On the other hand, Newman and his associates expressed the belief that they have demonstrated that environmental factors cause smaller differences between the two members of a pair of identical twins than between fraternal twins. But since the external influences themselves were so variable, it seems to me unjustifiable to use the responses to them as a basis for drawing conclusions.

57. von Verschuer, O.: Ergebn. d. inn. Med. u. Kinderh. **31**:35. 1927.

58. Newman, H. H.; Freeman, F. N., and Holzinger, K. J.: Twins: A Study of Heredity and Environment, Chicago, University of Chicago Press, 1937.

While it is freely admitted that such features as height, the sweep and contour of the body's lines and the color of eyes and of hair are transmissible characters, one hesitates to believe that the weight of a human being is determined by inheritance, because, as I have emphasized in this monograph, weight is so easily and greatly altered by environmental conditions. It may be true that a good or a poor appetite is an inherited feature and that given identical environment those persons born with the good appetite would become obese. But the environmental experiences to which a person is exposed are highly varied, and his desire for food is greatly affected by the character of his world. It will be conceded that fashion is a potent determiner of weight. Has not the urge to be slim so governed the appetite that the young women of America are underweight, and have they not succeeded in training their appetites so that they habitually do not partake of food in excess of the small amounts that will just maintain their slight bodies? Does not the big business man, who considers portliness one of the attributes of his success, acquire and maintain a generous girth by indulging in rich and sumptuous meals?

Why did a little boy whose weight had been normal, become obese, self centered and dull subsequent to an attack of scarlet fever when a physician had informed his mother that her son's heart had been damaged by the infection and that he must remain in bed for months and subsequently must be trained to avoid activity? Why did he again lose weight some years later when boys at a preparatory school laughed at his feminine appearance, and why did he go in for athletics after another physician assured him that his heart was normal? Surely these are not inherited responses.

It must be concluded that one of the reactions of the human being, so responsive to the flood of stimuli impinging on him, takes place in the sphere of appetite and that obesity is a product of his environment.

Summary.—It is hoped that the foregoing discussion has convinced the reader that obesity is never directly produced by increased or diminished activity of an endocrine gland. In other words, no internal secretion is capable of so changing the metabolism that the total amount of fat in the body will increase unless the inflow of calories is greater than the outflow.

It remains for the future to decide whether a hypothalamic disorder or other cerebral disease is capable of causing human obesity through abnormal stimulation of appetite. Whatever the answer, the simple principle will remain that obesity is invariably the result of a disproportion between the inflow and the outflow of energy. The former must always be greater than the latter; because either the intake has increased or the outgo has diminished.

The suggestion of von Bergman, so volubly defended by Bauer, that the fat cells of obese persons possess an abnormally great avidity for fat and an exaggerated capacity for retaining it finds no support in experiments designed to test its validity.

Body build is inherited; obesity is not.

HUNGER AND APPETITE

In the ideal state the living organism is directed by hunger to secure food in amounts sufficient to replenish the bodily materials that have been destroyed by oxidation or have been excreted. This primitive mechanism does not give rise to sensations which are primarily pleasurable. It is, so to speak, more business-like than that. With the passage of time hunger has come to be so closely associated with other feelings called appetite that the mind of man no longer distinguishes clearly between the two. Appetite, strictly speaking, is a sensation produced by happy memories. The desire for food may be the expression of real hunger, but it is more generally a response to habit or the anticipation of pleasure. It is modulated by the emotions to a striking degree. Fright, fear, sorrow, illness and displeasing sights and smells depress or even abolish it. It is stimulated by foods that give off pleasant odors, that please the eye and the palate. Happy recollections and good companionship are conducive to overeating. It may be that the long established habit of eating certain quantities of food has a more profound influence on the appetite than does the intervention of lessened physiologic needs associated with hypofunction of an endocrine gland. Most persons know the pain that must be endured when the old path is abandoned.

A number of writers have marvelled at the accuracy with which the appetite meets the bodily needs, because the weight of most healthy adults scarcely changes from year to year. It is stated in a well known textbook that a man 20 years old who weighs 75 Kg. will double his weight in another twenty years if he merely eats one butter pat (8.9 Gm. of fat) in excess of his caloric requirement every day. But the author apparently failed to take into account the enlarging surface area that accompanies increasing weight. Consider for example, a normal man who weighs 75 Kg. (165 pounds). He would be 5 feet 10 inches (178 cm.) tall, and his surface area would be 1.91 square meters. At age 20 his normal basal heat production would be 41 calories per square meter per hour. Accordingly, this hypothetic person would have a basal heat production of 1,880 calories per twenty-four hours. If he consumed 80 calories a day in excess of his maintenance requirements, the resulting gain in weight would be accompanied by an increase in the area of his surface, which would become 1.98 square meters when his

weight had reached 81 Kg. The corresponding normal basal metabolism would now be 1,956 calories per twenty-four hours, instead of 1,880 calories. The calories yielded by the extra butter fat would then merely furnish the heat of the increment in basal metabolism, and the subject would no longer store fat unless he made another addition to his diet. The solid line in figure 8 shows the lessening gain in weight correspond-

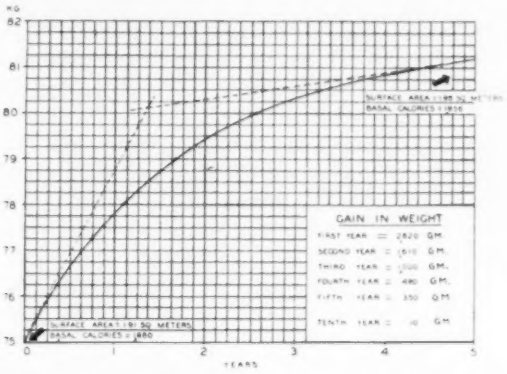

Fig. 8.—Weight plotted against time, with an initial dietary excess of 80 calories per day.

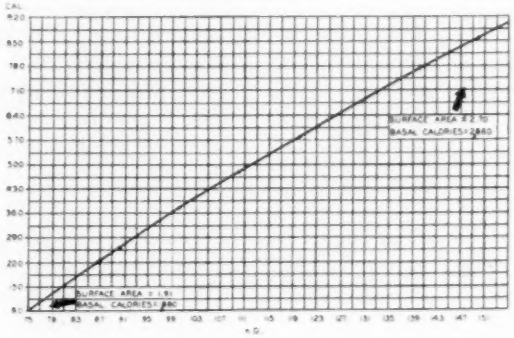

Fig. 9.—Excess calories plotted against weight.

ing to the increasing surface area. The broken lines indicate the rate at which weight would be added in the first and in the fifth year. Figure 9 shows how the diet would have to be progressively increased in order to permit the subject to continue to add to his weight at the rate at which he did so during the early weeks when the forbidden butter pat was actually furnishing 80 calories in excess of his requirement. By the time the man had doubled his weight, he would have increased his diet by 990 calories, not 80.

These calculations assume that the activity of the subject remains constant through the years and that the added weight does not lessen his efficiency.

Inaccuracy of Appetite.—Harrington [59] has been interested in the inaccuracies of the appetite. She has devised experiments that test its capacity to supply a subject with the right number of calories when he is offered different types of food. Three meals a day were served, and more food was offered than was consumed. The subjects were asked to eat as much as they desired, but they were given no information about the composition of the diets, all of which were adequate. The standard diet contained 1.5 to 2 calories per gram. A bulky diet was prepared by omitting concentrated foods and emphasizing fruits and vegetables. It contained 1 calory per gram. All subjects lost weight while taking it, because they ate only their habitual volume of food. The concentrated diet was constructed by substituting cream and butter for the milk of the standard diet and by increasing the sugar. It yielded 2.5 calories per gram. All subjects gained weight. They enjoyed this diet to the extent of eating more of it than was needed to satisfy the physiologic demands.

Harrington spoke of a patient who had had a thyroidectomy for exophthalmic goiter one year previously. Since then she had made a marked gain in weight. When she entered the hospital the second time her basal metabolic rate was 30 per cent below normal. She was kept on a diet of fixed composition and instructed to eat enough of it to satisfy her appetite. During the next eight days she took 2,450 calories a day and gained 900 Gm. Thyroid medication was then instituted. After the metabolic rate had become normal, her average intake was only 2,366 calories for eleven days, even though she lost 1,700 Gm. in these few days. Her appetite seemed to have lost contact with the fundamental requirements.

Another patient from Harrington's series is cited to emphasize how strongly appetite may be affected by the will. A girl 16 years old and 5 feet 7 inches (170 cm.) tall weighed 264 pounds (120 Kg.) when she entered the hospital. She was placed on a 1,000 calory diet and given careful instruction in its preparation. She lost 13 pounds (6 Kg.) in ten days. She returned six years later weighing 279 pounds (127 Kg.). This time she seemed to be in earnest because she had found that her size was such a handicap in securing a position. To learn whether her attitude toward food had really changed, she was offered a bulky diet containing 1 calory per gram. Each day she was served 4,000 grams of this diet, but she was given no instruction or information about the diet. For fifty-nine days her average intake was

59. Harrington, M. M.: J. Am. Dietet. A. **6**:101, 1930.

1,839 calories, and she lost 29 pounds (13 Kg.). The diet was next cut in half. Now she took 1,465 calories on the average for fifteen days. She was then discharged without instruction. During the next thirty days she lost 11 pounds (5 Kg.).

Evidently the primitive signals which notify the mind that it is time to restock the bunkers are often confused by emotional currents.

The matronly figure is not an unavoidable, although a common, sequel to the menopause. It does not mean that the secretions of the sex glands, now in abeyance, formerly had the power to restrain the growth of the adipose tissues. Rather does it indicate that the woman has reached that stage of life when she needs to strive less and finds more time for leisure. Even though she now needs much less food, she has more time in which to enjoy it and feels that she has earned the right to indulge herself. Probably she does not know or is but dimly aware that the candies she nibbles at the bridge parties which she so enjoys now that she is rested are adding their quota to her girth. Or if she is aware of the facts, she does not resist gain in weight, since the friends in whom she has the greatest confidence have assured her that nature intends her to lay on weight at this time of life. At first she still recognizes the signals that notify her that she has had enough to eat, but she deliberately ignores them because she has "toed the mark" long enough and from now on she is going to "humor herself." Gradually, the warnings become so blunted that she continues to enjoy gustatory pleasures until they are finally displaced by the discomforts attendant on ingestion of great excesses of food.

Emotional Craving for Food.—Other people grow fat because life has become more difficult for them, not less so. They are persons who are struggling with a problem—sexual, social or financial—for which they can find no solution. But they have discovered that they obtain temporary solace in eating. For them food acts as a balm, as alcohol does for others who find life too hard. We have seen many obese patients who either deliberately or without being aware of the situation have turned to food as a means of relieving pent-up emotions. The following case history is a good example of the development of obesity in a patient who strove to lessen the pain of overwhelming disappointment by incessant eating.

The patient was an unmarried woman aged 41, 5 feet 4½ inches (164 cm.) tall, who weighed 225 pounds (102 Kg.) when she entered the clinic. When she was 25 years of age she found herself deeply in love with a young man, but her father was firmly opposed to their marriage. During the next six months she battled with the problem whether she should obey her father, whose guidance she respected, or should disregard him. She finally decided in favor of the father. By this time she had become so disturbed emotionally that she could not bring herself to face the world. In order to avoid contacts, she refused to leave the second floor of her home for four years and remained in bed

most of the time. She gave no thought to the food that was brought to her by a servant except that she was aware of eating a great deal of sugar. The emotional instability became less marked after a time, and then she began to realize that she was causing her parents great pain and that she must once again take up the usual mode of life. At the beginning of the period of isolation she weighed 117 pounds (53 Kg.). When she emerged, her weight was 161 pounds (73 Kg.). She then went to a doctor for reduction of weight. He gave her a diet and 2 grains (0.13 Gm.) of thyroid daily. In less than a year her weight had diminished to 125 pounds (57 Kg.). Her father died suddenly shortly thereafter. At that time the family lived in a large house which they had previously been able to maintain generously, including the employment of servants. The patient now suddenly discovered that the family finances were in a precarious condition, and she decided that she must do all the work in the house. Even though there were only her mother and herself at home, she began her work at 4 o'clock in the morning and attempted to do all of the cleaning, cooking and laundering. She shortly found herself overwhelmed with fatigue, and the fear that she would be unable to continue the work caused her to attempt to gain strength by eating a great deal. Soon she disregarded the regular meal hours and ate whenever she felt exhausted. She continued to struggle on in this way for about a year, when her weight had reached 177 pounds (80 Kg.). And now she had to admit to herself that the large amount of food she had been eating had not helped her. In fact, she fatigued more easily than before and was hampered by shortness of breath. But she was chiefly disappointed because the obesity disfigured her. She tried to reduce her weight (without the aid of a physician), but she continued to gain nevertheless. When she realized that she was failing again, she became tense, restless and was harassed by insomnia. It seemed useless to make any further effort. Since she could calm herself temporarily by eating, she no longer resisted and ate whenever she felt distracted. She gained 50 pounds (23 Kg.) in less than a year. Then she concluded to make one more attempt to reduce her weight and came to the hospital for that purpose.

The examination disclosed no abnormalities other than the adiposity. She was instructed to eat all her meals in the special diet kitchen, where she received 450 calories daily. During the next four months she lost approximately 60 pounds (27 Kg.). After she adhered to the diet for a few weeks, the craving for food had disappeared and her appetite was satisfied. She was amazed.

About a month later she became emotionally upset and experienced a distaste for food. For a time she refused a good deal of the diet, but this episode lasted only a few days. Subsequently she adhered strictly to the plan and had no desire to eat more than she was offered. Accompanying the conviction that her weight would soon be normal again, a change in attitude occurred. She no longer worried and found that she was calm and philosophic.

The next case is another typical example of the use of huge quantities of food to assuage a seemingly hopeless situation. This time it was the physical and mental cruelty inflicted by a drunken husband.

The patient was 25 years of age when she entered the clinic. Her height was 5 feet 7½ inches (171 cm.) and she weighed 248 pounds (113 Kg.). She had been married six years previously to a man who was apparently a successful innkeeper. The first three years of married life were peaceful and pleasurable. Then, for no reasons evident to the patient, the husband began drinking heavily, took to gambling, neglected his business and went into debt. He became ill humored and

rough. To increase his income he converted the inn into a brothel and demanded that his wife, who was one of the waitresses, permit the male patrons to have sexual intercourse with her just as the other girls did. Her initial refusal was overcome by beating her so violently that she had to remain in bed for a week or two on numerous occasions to recover from the attacks.

She now noticed that for the first time in her life she was nervous and irritable and that she was annoyed by a gnawing sensation in her stomach. The latter discomfort was relieved by food, and she was gratified to find that large frequent meals made her better able to tolerate her lot. She now deliberately used food, wine and whisky to comfort her. It was not unusual for her to eat three large steaks a day and fill in the intervals with almost continuous munching of anything that caught her eye, and she "washed down" the solid foods with generous draughts of beer, interspersed with frequent gulps of wine and whisky. At the beginning of this period of overeating she weighed 148 pounds (67 Kg.). This was normal for her. During the next two and one-half years she gained 100 pounds (45 Kg.). She was divorced at about that time and has not gained since.

The examination disclosed a slovenly, unkempt young woman who suffered great emotional pain as she revealed her cruel experiences. She expressed great gratitude and relief when she began to feel that we intended to treat her in a dignified manner, that we understood her problem and that we were confident that we could make her a presentable young woman by reducing her weight to normal. She lost 17.1 pounds (8 Kg.) during the period of thirty-one days while she was an inpatient. She was discharged on a diet of 450 calories daily and has adhered to it without any difficulty.

Food Habits of Obese Persons.—Most recent writers have taken the position that obesity must be caused by a positive balance of energy. Since the expenditure of energy by obese persons is at least as great as that of normal persons, the law of conservation of energy demands an excessive inflow of calories to explain the adiposity. But it is perhaps possible that this law might be evaded by some metabolic aberration that has escaped detection. It is therefore important to study the food habits of obese persons as well as their dissipation of calories. A good deal of information about this question is available. In Lauter's [10] experience, patients suffering from "endocrine" forms of obesity consume amazing quantities of food exactly as do patients with obesity due to other causes. Dunlop and Murray Lyon [60] inquired into the dietary habits of a large group of patients. They found that an excessively large and poorly balanced diet was, among all the factors examined, the one most commonly present. Lambie [61] and Campbell [62] reported similar observations. Kisch [63] went further. He had 50 obese patients keep records of their food consumption. It ranged from

60. Dunlop, D. M., and Murray Lyon, R. M.: Edinburgh M. J. **38**:561, 1931.

61. Lambie, C. G.: Brit. M. J. **2**:885, 1935.

62. Campbell, W. R.: Canad. M. A. J. **34**:41, 1936.

63. Kisch, F.: Ztschr. f. klin. Med. **132**:504, 1937.

2,900 to 3,500 calories per twenty-four hours. Thirty patients who remained in bed were fed 200 calories in excess of their basal requirements. Twenty-eight of them complained of hunger. The obvious inference was that they had previously eaten much more.

Bruch [64] has made an exhaustive study of the food habits of 142 obese boys and girls, 2 to 13 years of age. She remarked that the tendency of the children and of their parents to minimize the food intake was encountered frequently but detailed questioning usually revealed the true picture. One mother, for example, who first answered, "Just normal, he doesn't eat much," later in the interview stated, "I know; I stuffed him like a goose." Nearly all the children had eaten excessive amounts of starchy food. She mentioned a boy of 10 who admitted six slices of bread, as sandwiches, a piece of cake, four apples and five bananas as a regular lunch, in addition to several glasses of milk. Not one child had learned to eat a mixed, well balanced diet. Vegetables and salads were the foods most frequently disliked. All children ate between meals whenever they felt like it. Bruch was convinced that the children became fat in all cases because they overate. She emphasized the close association between overeating and the lack of social maturation. Many of the children, for example, were incapable of dressing themselves. It was not unusual to learn that a child of 10 years was still being dressed and bathed by the mother and was not allowed to play with other children. This overprotection, which deprives the child of normal outlets, turns his attention to the satisfaction gained by eating. The obesity in other children dated from an upsetting experience. Often the fear that sexual development was abnormal had given rise to self pity and compensation in gluttony.

One is forced to conclude that obesity is invariably caused by eating more than the body needs, whether the patient be an adult or a child. Overeating is the expression of a habit or of a mood.

Hypoglycemia.—It has been suspected that the hunger caused by hypoglycemia has driven some patients to overeat and so become obese. This idea seemed to be supported by the observations of a number of investigators who reported that the appetite of emaciated patients could be stimulated by injections of insulin. However, Freyberg,[65] who attempted to confirm these observations, found that the whole effect was obtained through suggestion, since injections of solution of sodium chloride increased the appetite as successfully as insulin did. Further, he found that insulin had no effect on appetite unless the patients were informed that the medicine was given to help them eat more. Hypo-

64. Bruch, H.: Obesity in Childhood: III. Physiologic and Psychologic Aspects of the Food Intake of Obese Children, Am. J. Dis. Child. **59**:739 (April) 1940.

65. Freyberg, R. H.: Am. J. M. Sc. **190**:28, 1935.

glycemia is capable of causing great hunger in rats, but the level of blood sugar must be extremely low and continuously so. MacKay and Callaway [66] were unable to make rats fat by injections of regular insulin. It was necessary to maintain continuous and severe hypoglycemia by means of large doses of protamine zinc insulin in order to obtain fat rats. The blood sugar was kept at such a low level that the rats died when deprived of food for four hours. Barnes and Keeton [67] found it necessary to inject huge doses of protamine zinc insulin to obtain obesity. When 32 units per kilogram was injected twice daily, some rats gained 3 to 4 Gm. daily. But food had to be kept before them at all times to prevent death. Even so, the mortality was high.

Such profound degrees of hypoglycemia do not occur spontaneously in human beings, except in the decidedly infrequent cases of hyperinsulinism caused by tumors of the islands of Langerhans. We have recently seen a patient who had had one or more hypoglycemic convulsions every day for ten years. She had learned that eating was the only way to obtain any relief, but it was so short-lived that frequent feedings were essential. She became very obese. Operation disclosed multiple adenomas of the insular tissue.

If the common types of obesity are ever associated with hypoglycemia, the lowering of the blood sugar must be trivial, since it does not cause the classic symptoms of hypoglycemia and there is no evidence that the lesser grades of low blood sugar increase appetite. Furthermore, I am unaware that any one has demonstrated low blood sugar in patients whose main complaint was obesity. The determinations we have made on such patients have failed to reveal a low level of blood sugar in a single instance. On the contrary, hyperglycemia is commonly encountered. In fact, one writer stated that he finds high levels of blood sugar in nearly every patient who has been obese for twenty years.

THE FUNDAMENTAL CAUSE OF OBESITY

Many investigators have striven earnestly to discover why human beings become obese. During the era when methods for measuring energy metabolism were being developed, several prominent investigators became convinced, first that the basal metabolism of obese persons was abnormally low, then that their caloric response to food was lessened. However, further study with better methods has demonstrated that the energy performances of the obese person in both these phases are normal. In fact, it is now known that the presence of adiposity increases the total

66. MacKay, E. M., and Callaway, J. W.: Proc. Soc. Exper. Biol. & Med. **36**:406, 1937.

67. Barnes, B. O., and Keeton, R. U.: Am. J. Physiol. **129**:P305, 1940.

heat production. A fat person requires more food calories than his normal control merely to avoid loss of weight.

As the functions of the endocrine glands came to be understood and their key position was more clearly appreciated, it seemed to many leaders of the medical profession that hypofunction of the pituitary, the thyroid or the gonads offered an adequate explanation of the development of adiposity. But again further study has shown that this is not the cause. *Luxuskonsumption,* lipophilia and hypoglycemia have had the same fate.

These past efforts have not been wasted, however, for they have cleared the field for the acceptance of the doctrine that obesity is invariably caused by an inflow of energy that exceeds the outflow and that this disproportion is brought about by abnormality of the appetite. Excessive eating is an expression of a mood. It is a behavioristic response to a person's environment. This is not the place to attempt an analysis of behavior. For my purpose it will be sufficient to state that conduct is an exceedingly complex blend of hereditary acquisitions modified by earlier environmental experiences. This results in many different types of response by different persons when faced with seemingly identifical problems. One person suddenly faced by danger will run from it; the next one will attack it. Physical fatigue causes an insistent desire for food in some persons; other persons suffering from fatigue are repelled by food.

While no attempt is made to discuss the ultimate origins of behavior, the understanding of obesity will be advanced by making a list of proximate causes to which some persons respond (in part) by overeating: (1) overemphasis by a parent of the importance of food in a child's upbringing; (2) gratification obtained from the flavors of foods; (3) the feeling of repose and comfort produced by a full stomach; (4) the temporary respite from anguish caused by intellectual, social or sexual failure; (5) the food habits of youth which are carried over into middle age, even though the need for food is diminished, and (6) disabling disease with its lessened energy requirement which is compensated for by indulgence in food.

PREVENTION

Since obesity is an entirely preventable disease, people should be taught how to avoid it. A real effort to acquaint mothers with the dietary needs of their children would be a worth while addition to public health programs. School physicians ought to take the responsibility of teaching children the penalty of overeating. Physicians who are caring for patients suffering from chronic illnesses that limit activity should carefully plan the diet to avoid the insidious acquisition of excessive adipose tissue.

TREATMENT

Weight can always be reduced by adherence to a restricted diet, but cooperation by the patient is unlikely until the nature of obesity is elucidated and his particular reason for overeating has been discovered and explained to him. The chronicity of his ailment and its lack of immediately disabling features and of severe pain make it so easy to find excuses for delaying treatment or for being lax about it. Most patients are unaware of the threat to life that obesity entails, and they can scarcely be expected to take their condition seriously until they acquire the information.

Endocrine Medication.—Thyroid preparations are prescribed by physicians who attribute obesity to hypofunction of the thyroid gland, but it has been pointed out that the metabolic rate with few exceptions is normal and that the twenty-four hour heat production of obese persons is greater than that of persons whose weight is normal. It does not seem wise to burden the patient with the irritability and nervousness of hyperthyroidism and to add to the burden of a circulation already overloaded. Only when the occasional patient is encountered whose basal metabolic rate is pathologically low is thyroid medication justified.

There is serious objection to the administration of any endocrine preparation because the patient, already conditioned by the propaganda of friends and of advertising, is confirmed in his belief that he is the victim of a glandular disease. He is satisfied that the substitution therapy will reduce his weight and that the diet, in spite of the preachments of the physician to the contrary, need not be taken seriously.

Exercise.—Exercises of all sorts are widely advocated. These include massage and other passive exercises, but it surely must be realized that the muscular activity indulged in by the attendant is incapable of increasing the heat production of the patient. The latter must do the work if he is to dissipate the energy. But how much can be accomplished by muscular work? The mechanical equivalent of heat is 427 kilogram meters per calory. Since a human being is only about 25 per cent efficient, he will dissipate 3 calories as heat for every calory he converts to work. Accordingly, it will cost him 4 calories to raise 1,000 pounds (454 Kg.) three feet (91 cm.). If he weighs 250 pounds (114 Kg.), he can climb a flight of stairs 10 feet (305 cm.) high at the expense of but 3 calories. But by depriving himself of one third of a gram of butter or one fourth of a teaspoon of sugar, he will reduce his intake 3 calories. He will have to climb twenty flights of stairs to rid himself of the energy contained in one slice of bread! If he is a good walker he may dissipate 100 calories per horizontal mile. Omission of an ounce of cream will reduce the inflow

of calories to the same extent. Since adipose tissue yields 8 calories per gram, the mile's walk will reduce the patient's weight only 12.5 Gm. He must walk 36 miles (58 kilometers) to rid himself of 1 pound (0.5 Kg.) of adipose tissue—how disappointing! Exercise is usually a much harder way of reducing weight than by limitation of food.

Patients who derive pleasure from being muscularly active need not be restricted, provided they are not overtaxing their hearts. Wilder [68] has recently pointed out that some obese patients lose weight more rapidly while they remain in bed than when they are up. He stated the suspicion that they are suffering from lesser grades of passive congestion due to myocardial weakness and that the rapid decline in weight when they are confined to bed is due to loss of edema. Unfortunately, those who enjoy the exercise are also often the ones who acquire a ravenous appetite in the process and find it harder to adhere to a diet when they are active than when they are quiet.

Exercise may be harmful in still another way. When low calory diets are being used, most of the energy expended by the patient will be derived from body fat, and since the organism is restricted in its capacity to oxidize fat completely, this limit may be exceeded. Heat production of about 3,500 calories per twenty-four hours in a person receiving a 450 calory diet may be expected to cause acidosis. The pertinent facts in the most striking example of this condition that my associates and I have witnessed are recorded here:

Miss B., 24 years old and 5 feet 6½ inches (168 cm.) tall, weighed 289 pounds (131 Kg.) when she was admitted to the hospital for the treatment of obesity. During the next four weeks she was studied intensively on several reduction diets and was then placed on a diet that yielded 450 calories and consisted of protein 60 Gm., fat 10 Gm. and carbohydrate 30 Gm. Twenty days later, when her weight had fallen to 269 pounds (122 Kg.), she secured a room near the hospital but continued to come to the hospital for her diet. Since she enjoyed walking and knew that exercise would hasten the loss of weight, she strolled about considerably and gradually increased the length of the walks. One day she was on her feet, walking and shopping for eight hours. Late that afternoon, for the first time, she felt fatigued and had no desire for food. Nevertheless, she continued her activities that evening. Next morning she had no complaints but refused most of the noon meal and all of the evening one. By 10:30 p. m. she was definitely nauseated. She drank some orange juice but vomited it. She slept well that night. The third day she had no desire for food and ate little. That evening she felt ill generally. The fourth and the fifth day she stayed in bed and ate nothing. By the sixth morning she was so nauseated that she vomited every time she ate. Her vision was blurred; she had a pain in the pit of the stomach, and she was short of breath. These symptoms increased during the day, especially the nausea. And then for the first time, she reported her difficulties to her physician, who moved

68. Wilder, R. M.; Smith, F. H., and Sandiford, I.: Ann. Int. Med. **6**:724, 1932.

her into the hospital and gave her an intravenous injection of 3,000 cc. of a 5 per cent solution of dextrose in water. By the next morning she was still nauseated and fatigued, but the other symptoms were gone. Twenty-four hours later she felt quite well again.

Diet.—There is a considerable difference of opinion about how many calories the reduction diet should contain. Some authors have expressed the opinion that patients are less liable to cheat when only moderate restriction is prescribed. Our own experience has led my associates and me to the opposite conclusion. The slow loss of weight that accompanies the more liberal plans is so discouraging that the patients often give up the diet after a few months. We, like Evans,[69] have had most success when we have limited the calories sharply. The fear that the small diet will not maintain nitrogen balance has been set aside by Strang and McClugage.[16] They have shown that obese patients who subsisted on 450 calories daily were always in nitrogen balance when the diet contained 60 Gm. of protein. By choice, we prescribe a similar diet.

Selection of Food [70].—The reduction diet requires the use of milk, eggs, meat and meat substitutes, fruits and vegetables and whole wheat bread or whole grain cereal. Simple cookery is desirable, and the food should be prepared without the addition of fat. It is our experience that the dietary habits of obese people may be characterized not by an intake of a large quantity of food but rather by the use of moderate quantities of foods with a high caloric value. In the instruction of an obese patient, it is a simple matter to teach him to omit sugar because sweet flavors are not easily disguised. It is also relatively simple to teach him to limit the use of foods high in starch. Restricting of the intake of fat is a more difficult matter which requires special precautions in preparation and in cookery. The use of so-called "dietetic food" is usually not necessary.

The foods commonly used in low calory diets will be discussed here.

Milk: It is a good practice to use a pint of whole milk for each diet of 1,000 calories or over. Half of a large can of evaporated milk has the same food value as a pint of fresh milk. A pint of skimmed milk or of buttermilk has half the caloric value of a pint of whole milk and is used for diets containing less than 1,000 calories. Skimmed or separated milk obtained from the dairy contains only about 0.1 per cent fat. Pouring the cream layer from a bottle of milk will not give a product as low in fat as the dairy skimmed milk.

Meat and Meat Substitutes: Two servings each day should be used. Beef, veal, lamb and fowl are prepared by broiling, roasting and boiling.

69. Evans, F. A.: Tr. A. Am. Physicians **53**:352, 1938.

70. Frances MacKinnon, dietitian, University Hospital, guided me in the preparation of this section.

Lean cuts should be selected. The fat content is determined both by the type of animal and by the region of the body, as will be seen in table 19. The methods used for preparing meat are suitable also for fish. Fat is removed from canned salmon or tuna by scalding it with boiling water. Since shell fish are lower in calories than meats, their use should be

TABLE 19.—*Fat Content per Hundred Grams of Various Foods* *

0.1 to 2 %	2 to 5 %	5 to 10 %	10 to 15%
Fish	Fish	Fish	Fish
Bass	Bluefish	Butterfish	Halibut, smoked
Carp	Halibut steak	Eel	Herring, canned
Cod	Mackerel, horse	Herring, Atlantic	Mackerel, Atlantic
Croaker	Chicken	Lake trout	Mackerel, Spanish
Finnan haddie, smoked	Light meat	Salmon, canned	Salmon, Atlantic
Flounder, southern	Dark meat	Shad	Lamb
Haddock	Gizzard	Duck, domestic	Chops
Whiting	Liver	Muscle	Shoulder, lean
Perch	Duck, wild	Turkey	Beef
Pickerel	Muscle	Dark meat	Neck, very lean
Pike	Gizzard	Rabbit, domestic	Rib, very lean
Porgy	Turkey	Muscle	Roast, lean
Red snapper	Light meat	Veal	Sirloin
Smelt	Liver	Loin	Tenderloin
Sole	Rabbit, wild	Rib, lean	Tongue, lean
Sturgeon	Muscle	Round, lean	Venison
Shellfish	Veal	Rump, lean	Side and hind quarter
Clam	Kidney	Lamb	
Crab	Liver	Leg, lean	
Crayfish	Sweetbread	Beef	
Frog legs	Tongue	Brains	
Lobster	Lamb	Chuck, lean	
Mussels	Liver	Corned beef, very lean	
Oysters	Kidney	Dried beef	
Scallops	Beef	Foreshank	
Shrimp	Liver	Hindshank	
Miscellaneous	Pork	Kidney	
Cottage cheese	Kidney	Round, lean	
Tripe	Liver	Venison, lean	
		Goose, muscle	
		Guinea hen	
		Quail	

* Adapted from Chatfield, C., and Adams, G.: Proximate Composition of American Food Materials, Circular 549, U. S. Dept. of Agriculture, June, 1940. Articles high in fat have been omitted.

emphasized. Cottage cheese is the only cheese suitable for use in a diet with restricted calories; other varieties contain as high a percentage of fat as medium fat meat. Eggs should be boiled or poached to avoid the fat which is ordinarily used when they are fried or scrambled.

Vegetables (table 20): For diets of 800 calories or over it is well to prescribe at least three servings per day, one serving to be eaten raw. For diets of 800 calories or less, the vegetables can be chosen only from the 3 per cent and the 6 per cent list. Because of their vitamin and mineral values the daily use of leaves, stems or pods with a green color should be

stressed. In the cooking or serving of vegetables it is usual to add some form of fat. In the southern states salt pork is used in the cooking of greens and green beans. In the North butter is added to vegetables

TABLE 20.—*Fruits and Vegetables Classified According to Their Average Calorific Values per Hundred Grams* **

16 Calories	28 Calories	40 Calories
"3 per cents"	"6 per cents"	"9 per cents"
Carbohydrate, 3 Gm. Protein, 1 Gm.	Carbohydrate, 6 Gm. Protein, 1 Gm.	Carbohydrate, 9 Gm. Protein, 1 Gm.
Vegetables Asparagus Bamboo shoots Beans, green † Beans, wax † Bean sprouts Beet greens Broccoli Cabbage Cabbage, Chinese Cauliflower Celery Chard Chicory Cress, water Cucumbers Endive Escarole French endive Lettuce Mustard greens Radishes Sauerkraut Sorrel Spinach Squash, summer Tomatoes Tomato juice Turnip tops	Vegetables Carrots, canned Collards Dandelion greens Eggplant Kale Kohlrabi Leeks Lamb's quarters Okra Parsely Peppers Pumpkin Squash, winter Turnips Fruits Blackberries Melons Strawberries	Vegetables Brussel sprouts Beets Carrots, fresh Onions, fresh Peas, canned † Rutabagas Fruits Applesauce, canned, unsweetened Apricots, water-packed Blueberries Cranberries Gooseberries Grapefruit Grapefruit juice Peaches Pears Loganberries Limes Lemons Raspberries Tangerines
Fruit Rhubarb		
52 Calories	64 Calories	96 Calories
"12 per cents"	"15 per cents"	"18 per cents"
Carbohydrate, 12 Gm. Protein, 1 Gm.	Carbohydrate, 15 Gm. Protein, 1 Gm.	Carbohydrate, 18 Gm. Protein, 4 Gm.
Vegetables Lima beans, green, canned †	Vegetables Parsnips Kidney beans, red, canned † Peas, fresh †	Vegetables Corn, canned, sweet Potatoes
Fruits Apricots, fresh Cherries, sour, fresh Oranges Orange juice Pineapple Plums Kumquats	Fruits Huckleberries Grapes Mangos Nectarines	Fruits Prune juice Figs, fresh Grape juice Pomegranates

* Adapted from Chatfield, C., and Adams, G.: Proximate Composition of American Food Materials, Circular 549, U. S. Dept. of Agriculture, June, 1940.

Since tables like this were devised originally for use in prescribing diabetic diets, the foods are usually referred to in terms of the carbohydrate content. Thus any item in the first column is spoken of as a "3 per cent," not as a "16 calory" food.

† The protein content of these foods is distinctly higher than 1 Gm. per cent. Accordingly, they should either be omitted when weighed diets are prescribed or the additional calories should be taken into account. Green beans and wax beans contain 2.5 per cent protein, canned peas 4 per cent protein, canned green lima beans 5 per cent protein, canned red kidney beans 6 per cent protein and fresh peas 7 per cent protein.

before they are sent to the table. The people of southern Europe and Asia Minor cook vegetables in olive oil. Hence, obese patients should

be instructed that steaming, baking or boiling vegetables in salted water are the only methods of preparation to be used and that the vegetables should be served without the addition of fat.

Fruits (table 20): It is desirable to include two servings of low calory fruits each day, and preferably both should be eaten raw. Of the canned fruits, only those which are juice packed or water packed are suitable for use. In areas where housewives can their own fruit, it is a simple matter to add only water to the fresh fruits before the jars are processed. Contrary to popular opinion, a sugar syrup does not prevent spoilage of the fruit.

Bread: Since the refined bread flours have been deprived of the vitamins and minerals present in the whole seeds, it is desirable to urge the use of whole grain breads. However, since bread is a concentrated food, none of it is included in the 450 calory diet (table 21) and only one slice is prescribed in the 600 and the 800 calory diet (tables 22 and 23). Under such circumstances, even whole grain bread would be an unimportant source of vitamins. Furthermore, many patients dislike to eat whole grain bread. Fortunately, they can now obtain a product of nearly equal value in the form of "enriched" bread.

Fats: It is important to instruct the patient carefully with regard to the amount of fat which is to be added to his food. Butter or fortified margarines are the preferable forms to use, because even a small amount will add some vitamin A, while the meat fats and vegetable oils are devoid of this vitamin. For use in low calory diets, there are some palatable butter substitutes which are calory free.

Other Foods: Since clear tea and coffee, mushrooms and the soup made from bouillon cubes contain no calories, they can be used in any quantity desired. Saccharin is satisfactory as a sugar substitute. Salt, condiments and vinegar may be used as seasoning.

Since it is believed that the epigastric distress of which many patients complain is due to emptiness of the stomach, it is important to consider the distribution of the food. Even though three meals a day may not always conform to the patient's previous food habits, he will find that he gets hungry less frequently if he eats at least three times a day. Protein requires several hours of gastric digestion and therefore slows the emptying time of the stomach. The use of a food high in protein at each meal, such as an egg for breakfast and meat, fish or cottage cheese at luncheon and dinner, will keep the patient from having sharp hunger pains an hour or two after meals. If the meals are more than four hours apart, a quart of skimmed milk or buttermilk may be substituted for a pint of whole milk in the day's allowance and a glass of milk used at an interval half way between each two meals and at bedtime.

The matter of the measurement of portions calls for some comment. It is our experience that the use of dietetic scales, which weigh the food

in grams or ounces, is the best solution for a trying problem. These scales are simple to use, and food may be weighed directly in serving dishes without the extra handling necessitated by the use of cups. There are several inexpensive dietetic scales on the market, and usually they can be resold when the patient has completed his reduction of weight. The other and more commonly used method is prescribing foods in the ordinary household measure: cups, tablespoons and teaspoons. For many cooked vegetables, such as greens, tomatoes and diced root vegetables, measuring with a cup is satisfactory. For asparagus, broccoli, whole

TABLE 21.—*Reduction Diet, Four Hundred and Fifty Calories*
Protein 60 Gm., Fat 9 Gm. and Carbohydrate 32 Gm.

Menu Plan	
Breakfast:	
6 per cent fruit	100 Gm.
Skimmed milk	200 Gm.
Coffee	Ad libitum
Luncheon:	
Meat or fish	60 Gm. cooked
3 per cent vegetable	100 Gm.
Skimmed milk	100 Gm.
Dinner:	
Meat or fish	90 Gm. cooked
3 per cent vegetable	100 Gm.
Skimmed milk	100 Gm.
Sample Menu	
Breakfast:	
Melon	100 Gm.
Skimmed milk	200 Gm.
Coffee	Ad libitum
Luncheon:	
Boiled shrimp *	100 Gm.
Lettuce and tomato salad	100 Gm.
Skimmed milk	100 Gm.
Coffee	Ad libitum
Dinner:	
Lean corned beef	90 Gm. cooked
String beans	60 Gm. cooked
Cole slaw (raw cabbage with vinegar and seasonings)	40 Gm.
Skimmed milk	100 Gm.
Coffee	Ad libitum

* Note that 100 Gm. of shellfish has the caloric value of 60 Gm. of lean meat or fish.

beets or baked squash, attempting to measure with a cup spoils the appearance of the vegetable. It is almost impossible to measure raw vegetables satisfactorily, and the use of terms such as "medium" or "small" is leaving the size of the portion to the patient's judgment. It is also difficult to describe the sizes of servings of raw fruits, although one may use the diameters of round fruits or number of berries or grapes. The greatest difficulty arises in teaching the patient the sizes or portions of meat. Wax food models are helpful, but they are expensive and difficult to secure. However, for diets of 800 calories or more, the use of household measures and descriptive terms may suffice. When diets with fewer calories are prescribed, the patient needs a dietetic scale to insure precision in measuring portions.

Diet Prescriptions.—The plan for a diet restricted to 450 calories will be found in table 21. It also shows the selection and distribution of the actual food for one day. It will be noted that green leaves and fruits are emphasized. The bulk thus afforded compensates partly for the meagerness of the diet, and, of equal importance, these foods are excellent sources of the vitamins. However, any possible insufficiency of vitamins should be guarded against by prescribing additional amounts of the vitamin B complex. The 400 Gm. of skimmed milk supplies nearly

TABLE 22.—*Reduction Diet, Six Hundred Calories*
Protein 65 Gm., Fat 9 Gm. and Carbohydrate 65 Gm.

Menu Plan	
Breakfast:	
6 per cent fruit	100 Gm.
Bread	30 Gm.
Skimmed milk	100 Gm.
Coffee	Ad libitum
Luncheon:	
Meat or fish	60 Gm. cooked
3 per cent vegetable	100 Gm.
6 per cent fruit or vegetable	100 Gm.
Skimmed milk	200 Gm.
Dinner:	
Meat or fish	90 Gm. cooked
3 per cent vegetables	
1 raw	100 Gm.
1 cooked	100 Gm.
9 per cent fruit or vegetable	100 Gm.
Milk	100 Gm.
Tea or coffee	Ad libitum
Sample Menu	
Breakfast:	
Melon slices	100 Gm.
Bread, toasted, dry	30 Gm.
Skimmed milk	100 Gm.
Coffee	Ad libitum
Luncheon:	
Cottage cheese with olives	90 Gm.
Head lettuce (dressed with taragon vinegar and condiments)	100 Gm.
Raspberries	70 Gm.
Skimmed milk	200 Gm.
Dinner:	
Ground beef patty, broiled	100 Gm.
Beet greens with lemon	100 Gm. cooked
Sliced tomato	100 Gm.
Peaches, water-packed	100 Gm.
Skimmed milk	100 Gm.
Coffee	Ad libitum

0.5 Gm. of calcium, which is sufficient for an adult, and at the same time serves as a source of excellent protein. Practically all of the 60 Gm. of the protein prescribed are of animal origin. The fluid intake is not limited, since large amounts of liquid do not cause retention of water and restriction of fluids does not prevent it.

A diet of this type causes a loss of 3 to 5 pounds (1.3 to 23 Kg.) a week, on the average. The patient may be assured that he will lose 50 pounds (23 Kg.) in three or four months. After a few weeks when he is convinced that he is really losing at the promised rate, he finds it less trying to continue the plan. It is harder to follow a diet at home

than in the hospital where the food is put before the patient as a matter of course and without any expression of sympathy. This is especially true for the housewife who is responsible for feeding the family. The preparation of meals whets her appetite, and she must display great

TABLE 23.—*Reduction Diet, Eight Hundred Calories*
Protein 73 Gm., Fat 28 Gm. and Carbohydrate 65 Gm.

Menu Plan	Household Measure	Weight, Gm.
Breakfast		
6 per cent fruit	1 serving	100
Egg	1	50
Bread	1 slice	30
Butter	1 teaspoon	5
Luncheon:		
Meat or fish	2 oz.	60
3 per cent vegetable	1 serving	100
6 per cent fruit or vegetable	1 serving	100
Skimmed milk	1 glass	200
Butter	1 teaspoon	5
Dinner:		
Meat or fish	3 oz.	90
3 per cent vegetables (1 raw, 1 cooked)	2 servings	200
9 per cent fruit or vegetable	1 serving	100
Skimmed milk	1 glass	200
Butter	1 teaspoon	5
Sample Menu		
Breakfast:		
Strawberries	½ cup	90
Poached egg	1	50
Whole wheat toast	1 slice	30
Butter	1 teaspoon	5
Black coffee	Ad libitum	Ad libitum
Luncheon:		
Crab meat salad:		
Diced celery	¼ cup	60
Crab meat	½ cup	120
Minced onion and lemon		
Lettuce leaves		
Mayonnaise *	1 tablespoon	15
Melon	1	60
Skimmed milk	1 glass	200
Dinner:		
Beef steak, broiled	3 oz.	90
Asparagus	6 stalks	100
with butter	2 teaspoons	10
Lettuce salad:		
Lettuce	¼ head	50
Tomato	1 small	100
Dressing *	Ad libitum	Ad libitum
Pear	½ cup	120
Skimmed milk	1 glass	200

* Ingredients: 1 egg, 1 teaspoon salt, 1 teaspoon mustard, 2 cups liquid petrolatum, 2 tablespoons vinegar and ⅛ teaspoon paprika.

fortitude not to overstep her own meager allowance. For these reasons we urge the patients to experience the first two or three weeks of food restriction in the hospital. This also gives them the opportunity to acquire some information about the selection of food from the instruction provided for them.

When the need to lose weight is urgent, as, for example, in heart disease, we have not hesitated to restrict the diet to 300 calories. The patient in figure 10 was intensely dyspneic and deeply cyanotic when he

Fig. 10.—*A*, extreme obesity characterized by firm masses of adipose tissue. *B*, the same patient one year later. Dietary restriction has caused a loss of 286 pounds. The masses of adipose tissue are much smaller. *C*, the same patient after two years of dietary restriction. The total loss of weight was 366 pounds. The masses of adipose tissue are gone.

appeared for treatment. The circumscribed masses of adipose tissue in the pubic region and above the knees should be noted for they, together with the pain expressed in his face, would lead some clinicians to make a diagnosis of adiposis dolorosa (Dercum's disease). He was placed on a diet that contained 25 Gm. of protein and 300 calories. There was no

TABLE 24.—*Reduction Diet, One Thousand Calories*
Protein 75 Gm., Fat 42 Gm. and Carbohydrate 85 Gm.

Menu Plan		
Breakfast	**Household Measure**	**Weight, Gm.**
6 per cent fruit	1 serving	100
Egg	1	50
Bread	1 slice	30
Butter	1 teaspoon	5
Coffee ad libitum, with milk	1 oz.	30
Luncheon:		
Lean meat, fish	2 oz.	60
or		
Cottage cheese	3 oz.	90
3 per cent vegetable	1 serving	100
6 per cent fruit or vegetable	1 serving	100
Bread	1 slice	30
Butter	1 teaspoon	5
Whole milk	1 glass	200
Dinner:		
Lean meat or fish	3 oz.	90
3 per cent vegetables (1 raw, 1 cooked)	2 servings	200
9 per cent fruit	1 serving	100
Whole milk	1 glass	200
Tea or coffee	Ad libitum	Ad libitum

Sample Menu		
Breakfast:		
Strawberries	½ cup	100
Boiled egg	1	50
Whole wheat toast	1 slice	30
Butter	1 teaspoon	5
Coffee with milk	1 oz.	30
Luncheon:		
Cottage cheese	3 tablespoons	65
Kale	½ cup	100
Cabbage and celery salad	½ cup	100
Mineral oil dressing	1 tablespoon	15
Whole wheat bread	1 slice	30
Butter	1 teaspoon	5
Whole milk	1 glass	200
Dinner:		
Roast beef, fat trimmed	3 oz.	90
Broccoli	½ cup	100
Cucumber and radishes	¼ cup	50
Pear	1	125
Whole milk	1 glass	200
Black coffee	Ad libitum	Ad libitum

other treatment except rest. The excretion of nitrogen was about twice the intake of it. He adhered faithfully to this diet for one year, during which time he lost 286 pounds (130 Kg.). During the second year, he received 600 calories and lost another 80 pounds (36 Kg.). He had now returned to approximately normal weight. In the interval his gluttonous habits had been abolished, so that he continued to weigh 194 pounds (88 Kg.) without any effort to restrict his intake of food.

A few patients whose circumstances require them to work hard physically claim that the 450 calory diet reduces their strength so much

that they cannot continue their occupations unless they get more to eat. When we are convinced that they have given the diet an honest trial and that they cannot be persuaded to continue it some additional food is allowed. Often such patients can be satisfied with 600 calories arranged according to the plan in table 22. Still other patients cannot be persuaded to adhere to a diet unless they are allowed 800 or even 1,000 calories (tables 23 and 24).

The treatment of obesity in children must emphasize behavior rather than diet. It has been pointed out that these children have not learned to obey and that often they are pampered and uncooperative. It is an integral part of the treatment to teach them to control their whims and desires and to help them develop a sense of proportion. The younger children need to be trained to eat food that is wholly adequate for them without reduction of the energy content much below the requirement of normal children of the same height and age. Sharp underfeeding may be too great a load when coupled with the correction of behavior. If the calories of the diet are adjusted to stop further gain in weight, the obesity will gradually disappear as height increases. Later on, when the child has become adjusted to the discipline, a further reduction in calories may be arranged if there is still much extra fat to be removed.

News and Comment

1943 Annual Session of American College of Physicians Canceled.—The Board of Regents of the American College of Physicians has announced the cancellation of the 1943 annual session, which was scheduled to be held in Philadelphia April 13 to 16. This action was taken after thoughtful consideration of all factors involved, including an intimation from the Secretary of War and the Office of Transportation that large national medical groups should not plan meetings at the time set. The president has announced that all other activities of the College will be pursued with even greater zeal. The College will especially promote regional meetings over the country and will organize postgraduate seminars in the various military hospitals for physicians in the armed forces.

Book Reviews

Blood Grouping Technic. By Fritz Schiff, M.D., and William C. Boyd, Ph.D., with a foreword by Karl Landsteiner. Price, $5. Pp. 248. New York: Interscience Publishers, Inc., 1942.

The authors of this monograph are well qualified, as indicated by Landsteiner in the foreword. The book is divided into three parts: "Theoretic Foundation of Blood Grouping," "General Technic of Blood Group Investigation" and "Special Application of Blood Grouping Technics." The subjects are clearly and briefly discussed with the idea of aiding clinicians, serologists, anthropologists and workers in legal and in military medicine. Not only is the material presented clearly from a theoretic point of view, but it is presented practically, including the technics for typing blood for transfusions and for establishing paternity. The chapters, subchapters and paragraphs are numbered, so that by merely referring to the table of contents one can easily find any aspect of a subject. A fairly complete bibliography follows each subchapter for those who might be interested in further details of the original observations. There is a good index in addition to the rather complete table of contents.

This monograph will be appreciated by every one and is to be recommended not only as a reference book but as a book worth reading to learn much about blood types and typing technics and their practical applications.

The Ophthalmic Formulary. By G. Griffin Lewis, M.D., F.A.C.S. Price, $3.50. Pp. 167. Springfield, Ill.: Charles C Thomas, Publisher, 1942.

The compilation of "favorite prescriptions of prominent oculists from all parts of the world" is a handy gadget to have on the desk for an oculist who wonders what a distinguished colleague might prescribe for a given disease of the eye. Most of the formulas contained in this volume have the venerability of age and long usage and will stand the test of pharmacologic compatibility. A few will stand the test of therapeutic experience.

The name of a sponsor appears with every prescription. It is not claimed that the sponsor originated the formula or is responsible for the spelling or the accuracy of the dose. The purpose of the name is not clear, but one may assume that it implies that the formula was one of his favorite prescriptions.

Indications for use of the various prescriptions are given in a general way. Contraindications are not mentioned. The manual is useful as a crib from which a lazy physician may select and prescribe a remedy for a condition which he hopes he has diagnosed correctly (for otherwise the book fails to rescue him from his dilemma). It may also lend moral support to his efforts in treatment of diseases of the eye. In most instances he will find that the sponsor's name is as useful as the formula.

The Pathology of Trauma. By Alan Richards Moritz. Price, $6. Pp. 386, with 117 engravings. Philadelphia: Lea & Febiger, 1942.

As the publisher states, this book is designed to bridge the gap between the various pathologic and clinical disciplines dealing with trauma. The subject is thoroughly covered; after general chapters traumatic lesions of every system of the body are dealt with. As a matter of fact, the subject is treated so extensively that little space is available for individual subjects. No less important a matter than penetrating wounds of the thorax is, for example, discussed in one page. The illustrations are excellent and the bibliography representative.

INDEX TO VOLUME 70

Book Reviews are grouped together and are indexed under that heading in alphabetical order under the letter B.

Abdomen: See Gastrointestinal Tract
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